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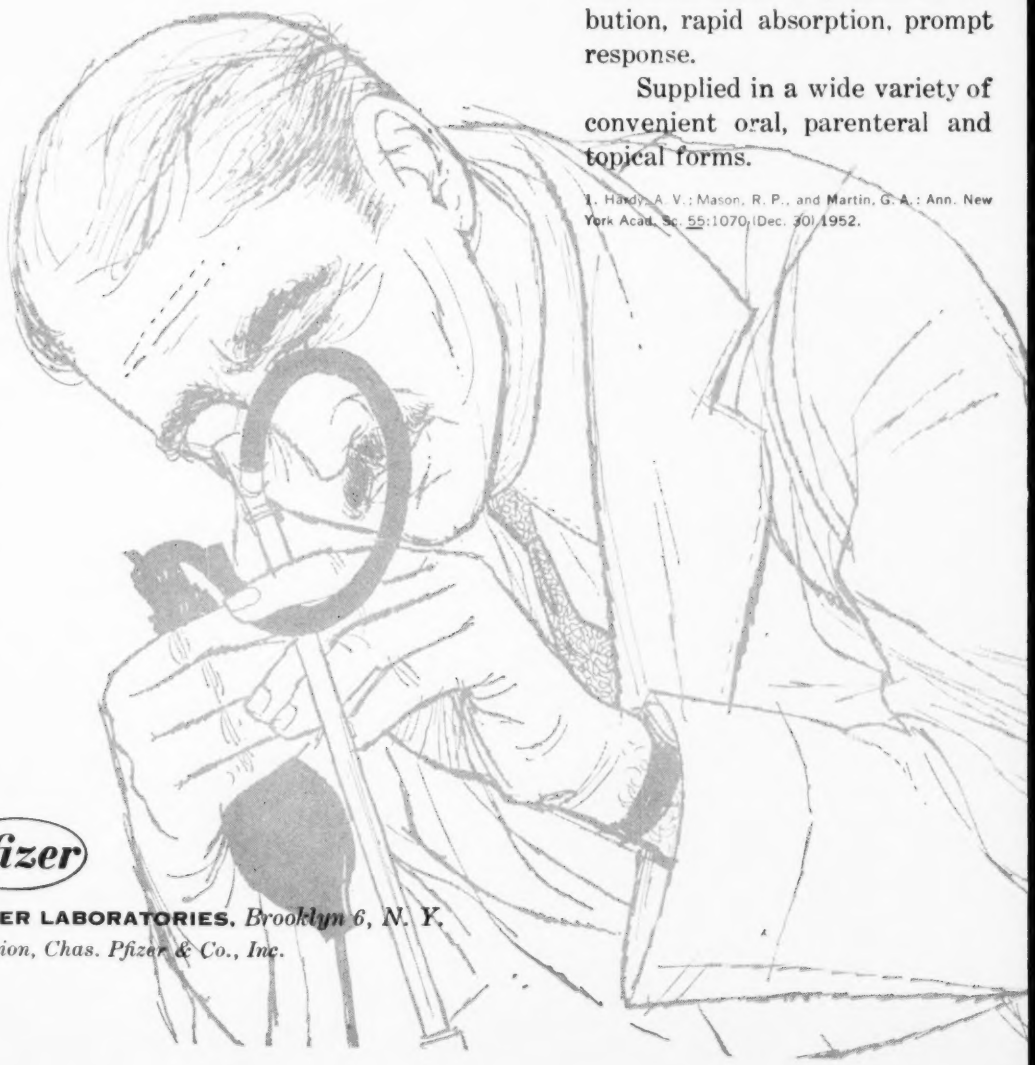

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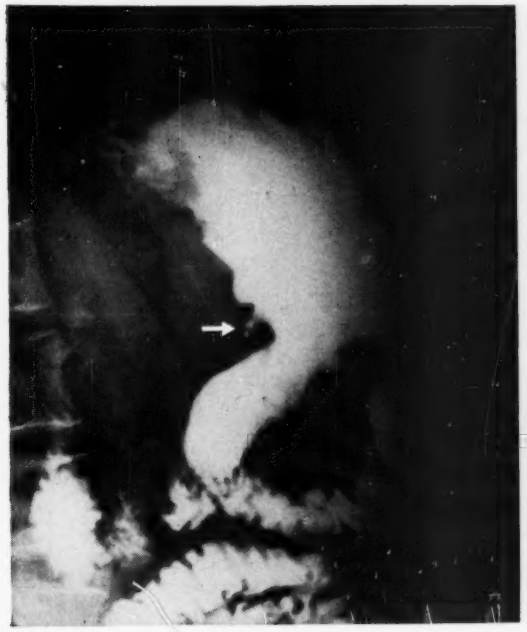

Fig. 1 "Roentgen examination . . . revealed the ulcer to be very much in evidence."

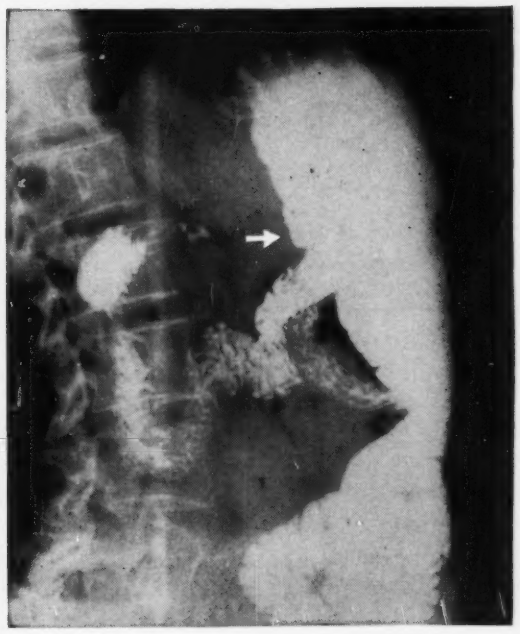

Fig. 2 In ten weeks "the ulcer niche was no longer in evidence roentgenologically or gastroscopically."

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1. Schwartz, I. R.: Personal communication, Feb. 9, 1953.

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VOL. 21, No. 2 FEBRUARY, 1954

THE American Journal OF Gastroenterology

(FORMERLY THE REVIEW OF GASTROENTEROLOGY)

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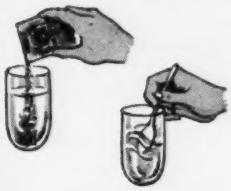

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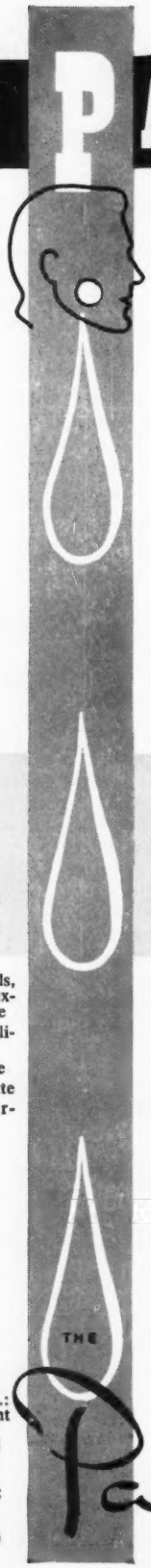

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Sandweiss, D. J.: W. P. Saunders, Phila., Peptic Ulcer, Chapter 28, 1951

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CLINICAL AND BIOCHEMICAL OBSERVATIONS ON THE USE OF LARGE DOSES OF TESTOSTERONE PROPIONATE IN ACUTE AND CHRONIC LIVER DISEASE*

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Seventeen cases of acute hepatitis and 26 cases of cirrhosis were studied during the administration of large doses of testosterone propionate. Marked clinical and biochemical differences in response became apparent between these two groups during this preliminary investigation.

High doses of testosterone were administered in acute and chronic liver disease to obtain maximal anabolic effects. The average total dose and duration of treatment in hepatitis and cirrhosis was approximately the same; 3.7 grams over a period of 12 days. Usually 500 mg. of testosterone propionate was administered intramuscularly for 2 days followed by daily doses of 300 mg. for variable periods. Table I outlines the total dose and duration of testosterone administration of the various groups studied.

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*Read before the Eighteenth Annual Convention of the National Gastroenterological Association, Los Angeles, Calif., 12, 13, 14 October 1953.

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Selection and Classification of Cases

The 44 patients in this study were observed on the medical wards of the Los Angeles County General Hospital during the year 1951. All patients received a standard diet containing approximately 125 gm. protein, 300 gm. of carbohydrate, 100 gm. of fat and 3 gm. of sodium. Vitamin supplements and sodium restriction to 500 mg. were additional measures instituted in the presence of edema or ascites.

In 5 of the 17 cases of acute hepatitis other diseases were present. These included the following: heart failure, diabetes mellitus, cholelithiasis, surgical removal of the pituitary and cholangiolitic hepatitis with questionable prostatic malignancy. Infectious hepatitis could not always be differentiated from serum hepatitis.

The cirrhotic group was further divided into 5 cases with subacute alcoholic cirrhosis; 19 portal (Laennec's) cirrhosis; 1 posthepatitis cirrhosis; and 1 xanthomatous biliary cirrhosis as outlined in Table III.

TABLE I

Average Total Dose and Duration of Testosterone Administration in Hepatitis and Cirrhosis

	Hepatitis		Cirrhosis					
	Acute (17)		Subacute (5)		Portal (20)		Biliary (1)	
	Gm.	Days	Gm.	Days	Gm.	Days	Gm.	Days
Average	3.7	12	6	18	3.7	12	7.2	24
Range	2-6	6-20	5-10	8-30	1-14	4-45		

Data and Methods

Objectives:—The primary objectives of this study were the following: (1) To compare the clinical and biochemical responses of patients with acute and chronic liver disease following the use of large doses of intramuscular testosterone propionate; (2) to obtain biochemical data relative to certain phases of lipid, steroid and creatinine metabolism; (3) to correlate, if possible, the biochemical patterns with the clinical course of the disease, and (4) to assay the value of the clinical and biochemical findings for potential prognostic and therapeutic purposes.

Biochemical Data:—All specialized 17-ketosteroid and creatinine studies were done by the Bio-Science Laboratory of Los Angeles. Chylomicron, cholesterol and phospholipid determinations were made through the courtesy of Dr. Willard Zinn[21]. The hospital laboratory performed routine liver profile studies including the following: cephalin cholesterol flocculation, thymol turbidity,

alkaline phosphatase, albumin/globulin, icteric index, urinary urobilinogen and bilirubin.

A "testosterone tolerance test" was used to determine the percentage of 1,000 mg. of testosterone propionate recovered in the urine as 17-ketosteroids. The details of this test are outlined below:

Day 1:—Twelve noon—patient empties bladder fully and this urine is discarded. All the urine passed during the next 24 hours is saved. Ten c.c. of xylene is added to each bottle as a preservative prior to collection. At 12 noon

TABLE II

SALIENT CLINICAL DATA IN 17 CASES OF HEPATITIS

Name	Age	Sex	Testosterone		Complications
			Total Dose (Gm.)	Days	
1. J. B.	37	Male	6.3	20	
2. J. P.	55	"	5.6	16	
3. R. G.	29	"	4.0	7	
4. L. B.	44	"	2.5	7	
5. S. L.	48	"	4.6	14	
6. P. N.	17	"	2.5	7	
7. R. S.	42	"	2.5	7	
8. A. S.	21	"	3.3	11	Fever
9. E. D.	25	Female	5.8	17	Hirsutism, voice change
10. H. C.	37	"	5.4	18	Hirsutism, voice change
11. L. H.	64	"	6.1	17	Voice change
12. S. W.	53	"	2.1	7	
13. W. W.	56	Male	5.5	17	Cholangiolitic hepatitis with questionable prostatic cancer
14. J. P.	57	"	2.2	6	Surgical removal of basophilic adenoma of pituitary
15. A. R.	77	"	2.5	7	Heart failure
16. M. M.	50	Female	2.1	7	Diabetes mellitus
17. R. S.	42	"	2.1	7	Cholelithiasis and cholangio-hepatitis

the next day (end of first 24 hour period), the patient is instructed to empty bladder and the urine is placed in sample for day 1. The first specimen is now finished and sent to chemistry.

Day 2:—Twelve noon—collection of the second specimen now starts. The patient is given 2.5 c.c. of testosterone propionate in oil (100 mg./c.c.) in each gluteus muscle*. Hence the patient receives a total of 500 mg. of testosterone propionate. At 12 noon, the following day, the patient empties his bladder and this urine is placed in specimen for day 2.

*Oreton (100 mg./c.c.) was furnished through the courtesy of the Schering Corporation.

Day 3:—Twelve noon—collection of third specimen now starts. Again at 12 noon, 5 c.c. (500 mg.) of testosterone is injected and the following day at 12 noon, the patient empties his bladder and this urine is placed in the specimen for day 3. The test is now completed.

TABLE III

SALIENT CLINICAL DATA IN 27 CASES OF CIRRHOSIS

Name	Age	Sex	Testosterone		Complications
			Total Dose (Gm.)	Days	
Subacute (Alcoholic)					
1. C. B.	46	Male	3.3	9	
2. A. G.	66	"	10.0	30	
3. J. G.	53	"	4.8	17	
4. E. H.	34	Female	6.3	21	Voice change, fluid retention +
5. J. N.	42	"	5.4	20	Voice change, acne
Portal					
1. F. T.	44	Male	8.4	28	Increased fluid retention 2+
2. B. M.	38	"	2.4	8	" " " 3+
3. J. R.	35	"	3.9	13	" " " 3+
4. D. C.	37	"	2.5	5	" " " 3+
5. H. H.	54	"	2.2	4	" " " 3+
6. C. H.	38	"	5.2	16	" " " 1+
7. G. D.	35	"	5.1	17	" " " 1+
8. A. W.	40	"	1.7	5	" " " 3+
9. T. B.	49	"	5.1	17	Voice change, mastodynia, fever, Increased fluid retention 3+
10. G. R.	59	"	2.2	6	" " " 3+
11. J. C.	64	"	2.5	7	" " " 1+
12. L. V.	37	"	1.6	4	" " " 1+
13. J. T.	50	"	2.4	8	" " " 2+
14. F. D.	44	Female	2.2	6	" " " 3+
15. G. B.	56	"	2.0	4	" " " 1+
16. C. R.	50	"	2.5	8	" " " 3+
17. A. M.	23	"	1.0	3	" " " 2+
18. G. G.	46	"	5.7	19	
19. M. S.	37	"	2.2	6	Increased fluid retention 2+
Posthepatitis					
1. A. O.	48	Female	13.5	45	Acne
Xanthomatous Biliary					
1. F. H.	56	Female	8.3	25	

CLINICAL OBSERVATIONS

The clinical response of patients with acute hepatitis and subacute alcoholic cirrhosis was similar. The total number of cases studied is insufficient for true statistical evaluation. These cases do present a significant pattern, however, which may be more readily visualized in a percentile form as shown in Table IV.

In 88 per cent or 15 cases of acute hepatitis a definite increase in appetite and sense of well-being was noted within 72 hours. In 34 per cent or 7 of these patients characterized by severe anorexia and lethargy, a dramatic improvement occurred. Treatment in this group was begun 5-18 days (average 12 days) after the onset of clinical jaundice. In 47 per cent or 8 additional cases where therapy was begun later, between 12-25th days (average 18 days) a less striking improvement occurred.

Two cases of acute hepatitis failed to respond. The first was a 77 year old male with arteriosclerotic heart disease and borderline cardiac decompensation who later developed progressive heart failure (A. R.). Autopsy showed hepatic

TABLE IV

PERCENTILE SUMMARY OF CLINICAL OBSERVATIONS ON THE EFFECT OF LARGE DOSES OF TESTOSTERONE IN ACUTE HEPATITIS AND CIRRHOSIS

OBSERVATIONS	HEPATITIS	CIRRHOSIS	
	ACUTE (17)	SUBACUTE ALCOHOLIC (5)	PORTAL (20)
INCREASED APPETITE AND SENSE OF WELL-BEING	(15) 88%	(5) 100%	(6) 40%
INCREASED LIBIDO	(11) 65%	(4) 80%	0%
INCREASED FLUID RETENTION	(1) 6%	(1) 20%	(18) 96%
HIRSUTISM	(2) 12%	0%	0%
VOICE CHANGES	(3) 18%	(2) 40%	(1) 5%
ACNE	0%	(1) 20%	(1) 5%
MASTODYNIA	0%	0%	(1) 5%
FEVER	(1) 6%	0%	(1) 5%

and adrenal necrosis as well as cardiac failure. The other patient was a 56 year old male with a consistently high acid phosphatase and a questionable prostatic malignancy, whose subsequent course indicated a severe cholangiolitic type of hepatitis.

The clinical response of 5 patients with subacute alcoholic cirrhosis was similar to acute hepatitis except where modified by concurrent infection and fluid retention. Improvement was noted between the third and seventh days in this group. On admission bronchopneumonia was manifest in varying degrees in all cases. Response to antibiotic therapy seemed enhanced by the use of testosterone. In A. G., who developed what appeared to be a terminal broncho-

pneumonia unresponsive to three weeks of hospitalization, routine supportive measures, and one week of penicillin therapy, rapid improvement followed with the addition of testosterone.

On the other hand, clinical improvement in appetite and sense of well-being in patients with portal cirrhosis appeared dependent on the control of fluid retention. Ninety-six per cent or 18 cases showed increased edema and ascites following the daily use of 300 mg. Thirty-five per cent or 6 cases with minimal pre-existing fluid retention improved with the concurrent use of mercurial

TABLE V

EXACT VALUES OF KETOSTEROID EXCRETION IN LIVER DISEASE FOLLOWING TESTOSTERONE

Acute Hepatitis	Patient	Sex	Age	17 Ketosteroids Mg./24°		% Conversion
				Day 1	Day 2	
	1. L. B.	♂	44	98	187	29
	2. L. H.	♀	64	94	163	26
	3. J. P.	♂	55	39	128	17
	4. S. L.	♂	48	96	160	26
	5. R. S.	♂	47	80	156	24
				AV.=80	AV.=158	AV.=23.8
Cirrhosis Subacute	1. C. B.	♂	46	66	109	17
Portal	1. J. R.	♂	35	7	13	2
	2. G. B.	♀	56	12	47	6
	3. D. C.	♂	37	19	29	5
	4. J. C.	♂	64	8	20	3
	5. H. H.	♂	54	26	71	10
	6. C. R.	♀	28	12	51	6
	7. F. D.	♀	44	23	81	10
	8. A. W.	♂	40	10	23	3
	9. C. R.	♂	59	32	58	9
	10. C. H.	♂	50	15	15	3
				AV.=15.3	AV.=40	AV.=5.5
Biliary	1. F. H.	♀	56	15	72	9

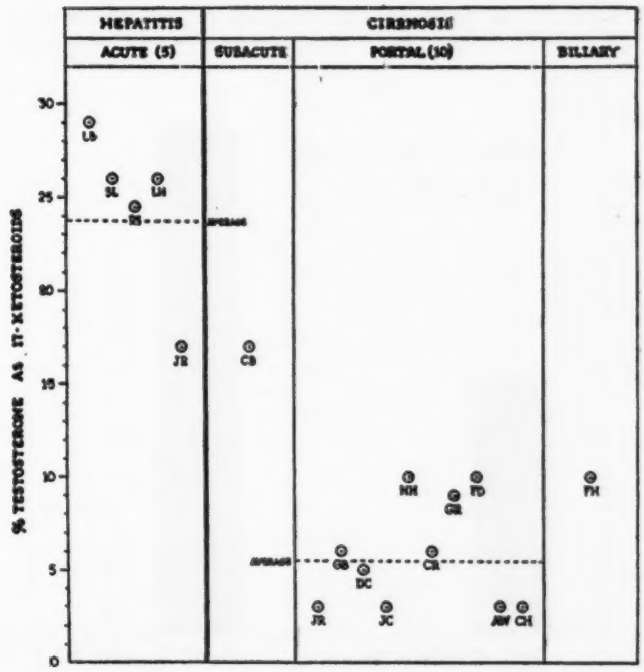
diuretics. Six cases with moderate ascites on admission became clinically worse and treatment was stopped because of increased fluid retention. The terminal course of 6 critical patients with marked ascites, remained unaltered. In only one patient with proven portal cirrhosis was no fluid retention found. Large doses of testosterone in this group may be of clinical value only when fluid retention can be controlled.

By contrast no evidence of fluid retention was clinically detectable in patients with acute hepatitis, in the absence of cardiac decompensation.

The fluid response in the subacute form of alcoholic cirrhosis was variable. In one patient (J. G.) who had been on a 500 mg. sodium diet without change in weight for 5 days, testosterone administration was followed by a prompt diuresis and a loss of 9 pounds within one week. Another patient (E. H.) developed ankle edema during the first 6 days of treatment. Therapy was continued, however, and within 12 days this patient gained an additional 10 pounds without ascites or edema. In the other 3 patients of this group no fluid retention was evident.

TABLE VI

PERCENTAGE RECOVERY OF TESTOSTERONE AS 17-KETOSTEROIDS IN HEPATITIS AND CIRRHOSIS



During the convalescent phase of acute hepatitis and subacute alcoholic cirrhosis certain hormonal changes became apparent. A definite increase in libido was noted by most males and females during the second or third weeks of treatment. In 5 of the 8 women in these two groups (3 acute hepatitis, 2 subacute alcoholic cirrhosis) masculinization of voice, acne, and hirsutism developed when the total dose exceeded 2 gm. On the other hand, patients with portal cirrhosis noted no change in libido. In only one male (T. B.) of 19 portal cirrhotics did marked hoarseness of voice, mastodynia, and a fever develop after treatment. These changes subsided when testosterone was stopped. One female patient with probable posthepatitis cirrhosis and hypothyroidism developed acne

after 12.5 gm. was administered. A low grade fever developed in one case of acute hepatitis while under treatment (A. S.).

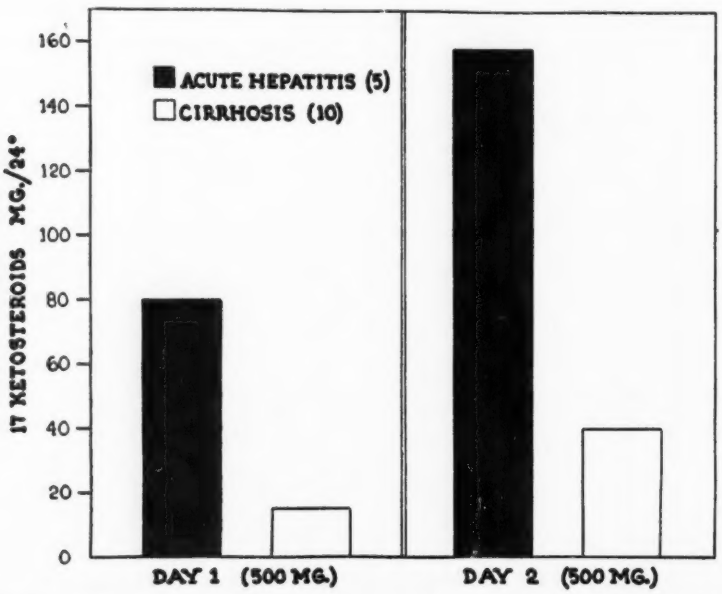
Biochemical Observation

A significant difference was observed in the ability of patients with acute hepatitis and portal cirrhosis to convert 1,000 mg. of testosterone propionate to 17-ketosteroids as is shown by Table V.

The total percentage of testosterone conversion in 5 cases of acute hepatitis averaged 23.8 per cent as compared to 5.5 per cent in 10 cases of portal cirrhosis. One patient with subacute alcoholic cirrhosis converted 16 per cent in contrast

TABLE VII

DIFFERENCE IN RATE OF CONVERSION OF TESTOSTERONE TO 17 KETOSTEROIDS IN ACUTE HEPATITIS AND CIRRHOSIS



to the patient with xanthomatous biliary cirrhosis where 10 per cent recovery was obtained as shown in Table VI.

Table VII illustrates the difference in the rate of conversion during the two days of the test. On the first day 80 mg. was the average excretion in 5 patients with hepatitis as compared with 15 mg. in 10 patients with cirrhosis; on the second day 158 mg. was excreted as compared with 40 mg.

Three complicated cases of acute hepatitis transformed 13, 9, and 5 per cent respectively: J. P. with a surgically removed basophilic adenoma of the pituitary, A. R. with heart failure and diabetes, and W. W. with cholangiolitic hepatitis and possible prostatic cancer.

Creatinine Metabolism

Six males with acute hepatitis excreted an average of 1.63 gm. of creatinine as compared with 0.85 gm. in 5 male cirrhotics. No significant difference was noted in the control and immediate post-treatment creatinine values of either group. One female patient with hepatitis excreted an average of 0.82 gm. In 5 women with portal cirrhosis the average creatinine excretion was 0.55 gm. These changes are shown with exact values in Table VIII and are diagrammatically represented in Table IX.

TABLE VIII

24 Hour Creatinine Excretion Before and After the Administration of 1,000 Mg. of Testosterone

Name	Age	Sex	Creatinine gm./24 Pre-Treatment	Post-Treatment
		Acute Hepatitis		
1. J. P.	37	Male	1.54	1.10
2. R.S.	22	"	1.86	1.80
3. L. B.	44	"	2.16	1.80
4. P. N.	17	"	1.56	1.17
5. S. L.	48	"	1.32	1.96
6. L. H.	64	Female	0.83	0.81
		Acute Hepatitis with Complications		
7. J. P.	57	Male	0.96	1.15
8. A. R.	77	"	1.01	1.03
9. W. W.	56	"	0.19	0.46
		Cirrhosis (Subacute)		
1. C. B.	46	Male	1.71	1.72
		Cirrhosis (Portal)		
1. J. R.	35	Male	0.67	0.35
2. D. C.	37	"	1.00	0.83
3. G. R.	59	"	0.92	0.67
4. B. M.	38	"	1.04	0.73
5. C. H.	53	"	0.94	1.45
6. G. B.	56	Female	0.08	0.57
7. M. S.	41	"	0.40	—
8. J. C.	43	"	0.70	0.48
9. C. R.	50	"	0.46	—
10. F. D.	44	"	0.81	0.76
		Cirrhosis (Xanthomatous Biliary)		
1. F. H.	56	Female	0.70	0.63

Two complicated hepatitis cases (A. R. and J. P.) excreted less creatinine than the average, but still more than the average cirrhotic male. The lowest recorded creatinine values were found in W. W.

In two cases of acute hepatitis (L. H. and J. P.) where large doses of testosterone were administered (4.0 gm.) a much higher creatinine excretion and creatinine coefficient was observed several days after medication was stopped. A "rebound" toward normal 24 hour excretion followed the reinstitution of testosterone as is shown by creatinine coefficient values in Table X.

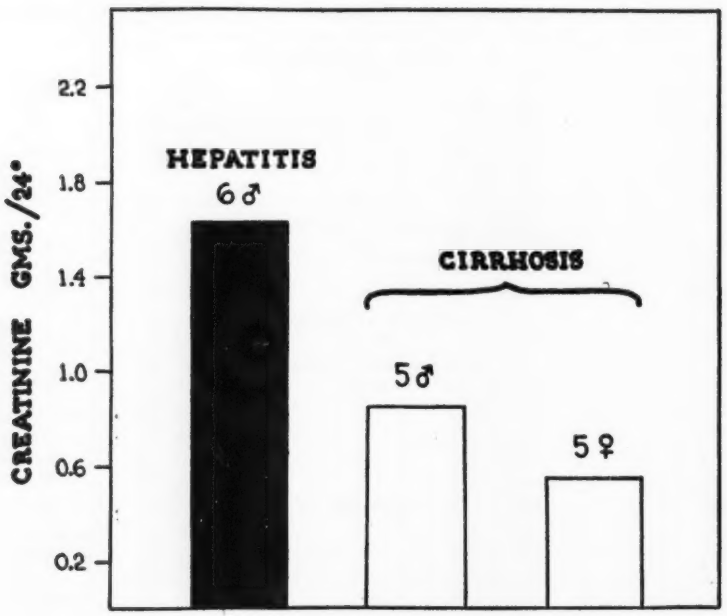
A similar rebound pattern was presented by R. S. with hepatitis, however, the pre-treatment creatinine excretion and coefficient was higher than the normal.

Two patients with decompensated portal cirrhosis (J. R., C. F.) had extremely low creatinine coefficients, and testosterone appeared to depress these values further. Persistently low creatinine coefficients were found in xanthomatous biliary cirrhosis in the absence of ascites or edema.

The clinical and biochemical findings are illustrated by the following case histories and tables.

TABLE IX

DIFFERENCE IN CREATININE EXCRETION
IN HEPATITIS AND CIRRHOSIS



ACUTE HEPATITIS

Case 1, Serum Hepatitis:—A Caucasian male (J. B.), aged 32, had generalized malaise, backache, dark urine, nausea and vomiting for 7 days before admission. Intramuscular penicillin and potassium permanganate soaks had been given intermittently over a 9 month period for a chronic dermatitis of the hands.

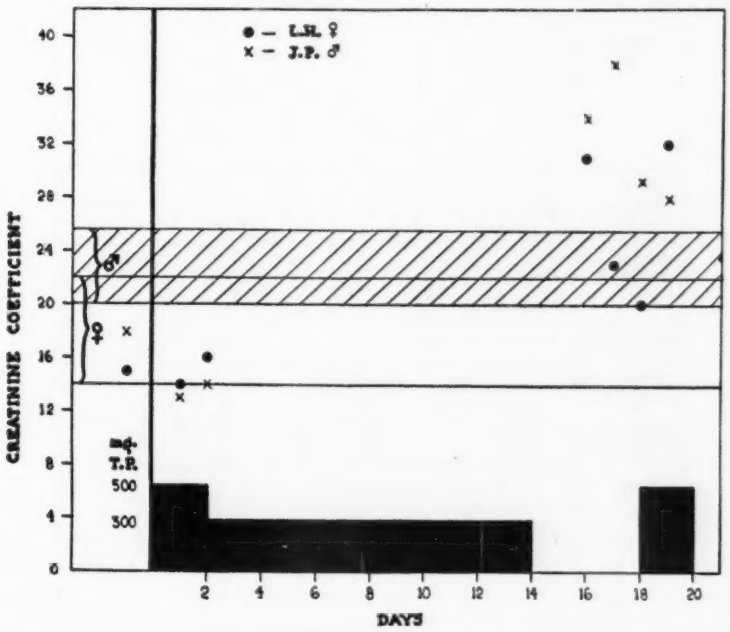
Physical Examination revealed a well-developed, well-nourished male who was lethargic, depressed, anorexic and jaundiced. Further examination disclosed a blood pressure of 155/96; temperature of 99.8°F.; pulse 100; weight 160 pounds; a tender liver enlarged to 3 inches below the right costal margin in the mid-clavicular line; and dermatitis of both hands.

Total dose:—6.3 gm. (20 days).

Course:—Approximately 72 hours after testosterone was given, a striking improvement was noted in mental outlook, sense of well-being and appetite. A ravenous appetite developed and 10 pounds were gained during the first 2 weeks of therapy. Libido was increased during the second week; the liver was no longer palpable. With the substitution of normal saline for testosterone for 5 days, no clinical change was observed (23-27 days), but a decrease of one and one-half pounds in weight occurred. On resumption of therapy for 8 days, no significant change in weight occurred. Four days after discontinuing treatment, 5 additional

TABLE X

HIGH CREATININE COEFFICIENTS IN HEPATITIS FOLLOWING LARGE DOSES OF TESTOSTERONE PROPIONATE AND THE "REBOUND" PHENOMENA



pounds were gained. The routine liver profile and certain electrolyte changes are diagramed in Table XI.

Final evaluation six months later showed an asymptomatic active individual weighing 175 pounds.

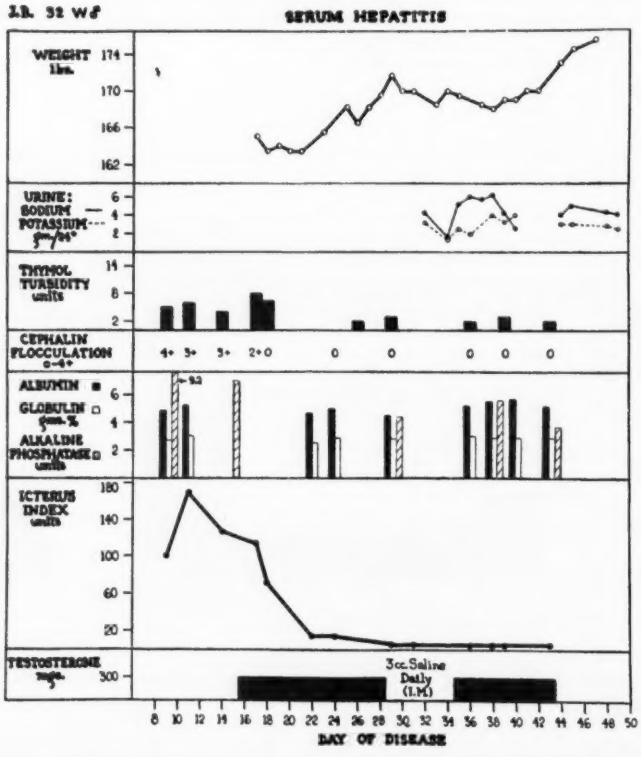
Comment:—This patient was extremely toxic before testosterone was given and showed striking clinical improvement within several days. A weight gain of 10 pounds occurred during the first 2 weeks. Subsequent testosterone therapy during the convalescent period did not increase the body weight, however, a progressive gain of weight developed upon cessation of treatment. The return

of the abnormal cephalin flocculation to normal on the 17th day after clinical icterus was earlier than is usually seen. No evidence of urinary sodium retention was observed while this patient was on an unrestricted diet during convalescence. The 24 hour urine volumes remained high (above 3,000 cml.) during and following therapy.

Case 2, Infectious Hepatitis:—A white female (L. H.), aged 64, complained of generalized malaise, anorexia, epigastric fullness, dark urine, yellow sclerae, and mental depression for 3 weeks prior to hospitalization. No history of parenteral injection or significant antecedent fat intolerance was elicited.

TABLE XI

CHANGES OBSERVED IN UNCOMPLICATED SERUM HEPATITIS
CASE 1 (J. B.)



Physical examination disclosed a well-developed and nourished female who was lethargic and deeply jaundiced. Palmar erythema, a tender liver 1 inch below the right costal margin in the mid-clavicular line, were other significant findings.

Total dose:—6.1 gm. (17 days).

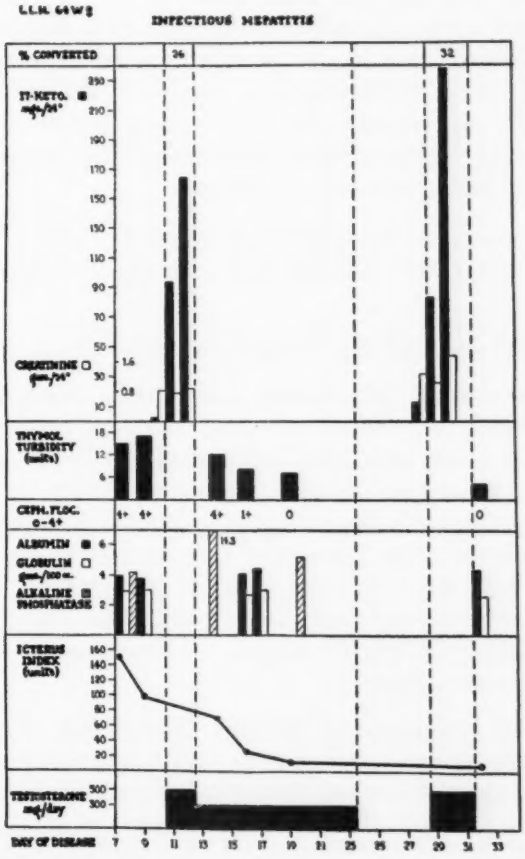
Course:—Within 48 hours after receiving 1,000 mg. of testosterone propionate, a striking improvement occurred in this "toxic" patient characterized by

restoration of appetite, improved mental alertness and sense of well-being. Transitory "tingling sensation" in the breasts were observed on the third day. In spite of a ravenous appetite a weight loss of three and one-half pounds occurred during a period of 21 days.

A return of libido and slight huskiness of voice were observed on the 13th day of treatment (4.3 gm.). These subjective changes were still present 46 days

TABLE XII

CHANGES OBSERVED IN UNCOMPLICATED INFECTIOUS HEPATITIS
CASE 2 (L. H.)



after this steroid had been discontinued. The liver was palpated 1 inch below the right costal margin 2 weeks after the institution of therapy. The laboratory data are diagrammatically presented in Table XII and illustrates the following:

A progressive decrease of the icteric index to normal; a rapid decrease of the cephalin flocculation (from 4+ [day 14] to 1+ [day 16]), a reduction of thymol turbidity from 17 to 4, an increase in the serum albumin and a decrease

in globulin, 26 per cent and 32 per cent conversion of testosterone propionate to 17 ketosteroids on the 11th and 27th days of jaundice respectively. The creatinine excretion which initially was in the lower limits of normal became excessively high 3 days after 4.0 gm. of testosterone was given. Readministration of testosterone lowered this value.

Comment:—Significant observations include: rapid improvement of anorexia, mental apathy, persistence of vocal and libidinous changes after therapy, relatively high testosterone conversion, and increased creatinine excretion after 4.0 gm. of testosterone.

Case 3, Serum Hepatitis:—A white female (H. C.), aged 37, had pruritus, yellow sclerae, dark urine and epigastric fullness for 8 days prior to hospitalization on May 24, 1951. Three months previously menometrorrhagia and a rapid gain of 30 pounds were indications for a currettement. The endometrial biopsy showed a markedly hyperplastic and proliferative endometrium. Postoperative bleeding necessitated the use of three whole blood transfusions. Excessive weight and facial hair had been present from puberty.

Physical examination on admission showed marked obesity, jaundice, hirsutism, and a tender liver 2 inches below the right costal margin in the midclavicular line.

Total dose:—6.9 gm. (300 mg. dosage over 23 days).

Course:—Improvement in appetite and mental alertness were apparent within 48 hours after treatment. An increased frequency of shaving, deepening of voice, and elevated libido were observed approximately 12 days later. The liver was no longer felt. The above complications progressed in the absence of further injections and necessitated further diagnostic studies 1 month after testosterone had been discontinued. The laboratory tests and x-ray findings were within normal range: icteric index 9 units; alkaline phosphatase 2.8 units; cephalin flocculation negative; thymol turbidity 4 McLagan units; albumin/globulin 5.4/2.8; protein bound iodine 4.7 mcgm.; 17-ketosteroids 10.7 mg.; creatinine 3 gm.; skull x-rays were negative.

In view of the progression of findings Ethinyl Estradriol (0.05 mg.) was started with noticeable clinical regression within a week and a return to pretreatment status at the end of 3 weeks.

Final evaluation:—Nine months later reexamination disclosed an obese healthy female with normal menses.

Comment:—This patient with pre-existing hirsutism developed progressive masculinization with large doses of testosterone which continued after treatment was stopped until a synthetic estrogen reversed the picture.

Case 4, Probable Serum Hepatitis and Diabetes Mellitus:—A white female (M. M.), aged 50, entered the hospital June 2, 1951 with a five day history of

jaundice, and generalized weakness. She had whole blood transfusions following surgery approximately 6 months ago.

Physical examination showed the following: blood pressure 160/88, a non-palpable liver, tenderness in right upper quadrant, varicose veins of the legs, and fungus infection of the feet.

Laboratory tests on admission revealed a fasting blood sugar of 290, urine sugar 3 plus, cephalin cholesterol flocculation 4 plus, thymol turbidity 11 units, and albumin/globulin 4.4/2.7.

Total dose:—2.1 gm. (7 days).

TABLE XIII

BIOCHEMICAL CHANGES OBSERVED IN COMLICATED INFICTIOUS HEPATITIS
CASE 4 (M. M.)

M.M. 50 W ♀ ACUTE HEPATITIS - DIABETES MELLITUS

CHYLOMICRONS					56				67		
CHOLESTEROL (Total)					352				227		
LIPID PHOSPHORUS					17.5				10.5		
C/P RATIO					1.4				1.2		
ICTERUS INDEX	62	62			21		11		9		
ALKALINE PHOSPHATASE					5.5				1.7		
CEPHALIN-CHOLES. FLOCCULATION		4+	4+		2+		0		0		
THYMOL TURBIDITY			11		9		6		5		
ALBUMIN		4.4			3.6		3.7		4.6		
GLOBULIN		2.7			3.5		3.6		2.6		
BLOOD SUGAR (Fasting)	290	220	188								141
URINE SUGAR	3+	3+	1+	1+	0	0	0	0	0		
TESTOSTERONE PROPIONATE						300 mgs.					
DAY OF JAUNDICE	4	6	8	10	12	14	16	18	20	22	28

Course:—The patient was placed upon a diabetic diet and given no insulin. Apathy and malaise persisted and testosterone was started on the 9th hospital day and was followed by clinical improvement. Table XIII outlines certain biochemical changes observed.

The cholesterol dropped from 352 to 227, phospholipid from 17.5 to 10.5 altering the C/P ratio from 1.4 to 1.2. No change occurred, however, in the persistently elevated chylomicron count. The cephalin cholesterol returned from 2 plus to zero, while the thymol turbidity dropped from 9 to 5 units. The albumin/globulin ratio improved from 3.6/3.5 to 4.6/2.6. A standard 3 hour 100 gm. glucose tolerance curve 1 week after testosterone therapy gave the following values:

141 mg., 300 mg., 184 mg., 122 mg. No insulin was given and 4 months later the patient was asymptomatic and the routine liver profile was normal.

Comment:—The following changes in a diabetic with hepatitis are of interest: continued symptomatic recovery without insulin, biochemical improvement in cholesterol, phospholipid, and glucose metabolism, albumin synthesis, high fasting chylomicron counts unaltered by testosterone.

Case 5, Acute Cholangio-Hepatitis Secondary to Cholelithiasis:—An obese white female (R. S.), aged 42, was admitted to the hospital on June 22, 1951 giving a history of sharp right upper quadrant pain radiating across the upper abdomen, and to the right flank for 9 days. She had previous similar attacks. Four days ago her urine became very dark. No chills or fever were noted.

TABLE XIV

CHANGES OBSERVED IN COMPLICATED CHOLANGIO-HEPATITIS
CASE 5 (R. S.)

R.S. 42 W ♀

ACUTE CHOLANGIO-HEPATITIS-CHOLELITHIASIS

CHYLOMYCRONS					50				32	35		
CHOLESTEROL (Total)					273							
LIPID PHOSPHORUS					12.1							
C/P RATIO					1.3							
ICTERUS INDEX	66		76	37			18	20				10
ALKALINE PHOSPHATASE	9.5			9.5				7.3				
CEPHALIN-CHOLES. FLOCCULATION	4+		4+	3+				3+				0
THYMOL TURBIDITY	17		24	28				11				8
ALBUMIN	4.2		4.0	4.3			5.3	4.8				4.3
GLOBULIN	3.0		3.1	3.7			3.9	3.3				3.2
TESTOSTERONE PROPIONATE							300 mg./day					
DAY OF JAUNDICE	4	6	8	10	12	14	16	18	20	22	24	26

Physical examination disclosed the following: icteric sclerae, moderate tenderness in the right upper quadrant, a tender liver palpable at the right costal margin, blood pressure 120/82, temperature 98.8° and pulse 80.

Laboratory tests on admission showed urine urobilinogen 1/80, urine bilirubin 2 plus, icterus index 66, alkaline phosphatase 9.5, cephalin cholesterol flocculation 4 plus, thymol turbidity 17, and an albumin/globulin of 4.2/3.0.

Total dose:—2.1 gm. (300 mg. for 7 days).

Course:—Testosterone was given 9 days after admission because of anorexia and apathy. The maximal temperature was 1°F. Appetite, sense of well-being improved rapidly. A progressive increase in libido was noted by the end of the

7 days of treatment. The patient was discharged 5 days later and the liver profile was essentially normal with the exception of a borderline icteric index of 11 and a globulin fraction of 2.9 gm. Cholecystography on September 17, 1951 demonstrated two gallstones.

Cholecystectomy was subsequently performed on October 13, 1951. A liver biopsy was taken during surgery and the microscopic examination showed "mild ascending cholangitis but no evidence of cirrhosis". "Mild chronic cholecystitis" was found in the gallbladder (Weldon K. Bullock, M.D.).

Fig. 1

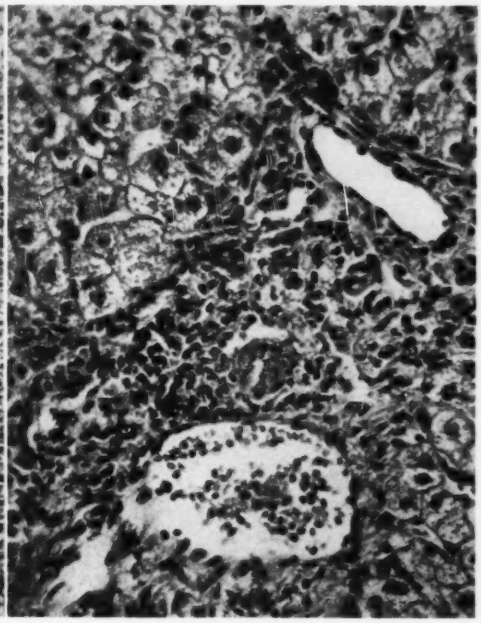


Fig. 2

Comment:—The following points are emphasized: that in a nonfebrile hepatitis due to cholelithiasis clinical improvement in appetite, mental depression and an increased libido may occur; the potential significance of a persistent mild chemical icterus and globulin indicating cholangitis, and the value of the history and cholecystogram in the diagnosis.

Case 6, Subacute Alcoholic Cirrhosis, Bronchopneumonia:—A white male (C. B.), aged 46, noted anorexia, icteric sclerae, dark urine, and gray stools for 7 days prior to admission on October 16, 1951. He gave a history of imbibing heavily of wine and whiskey prior to this third entry. Initial hospitalization on August 17, 1950 was followed by 4 days of shaking chills, fever, vomiting and deep jaundice. On discharge two were considered infectious hepatitis and alcoholic cirrhosis. Six months later a similar episode developed and a cholecystogram taken at this time was normal.

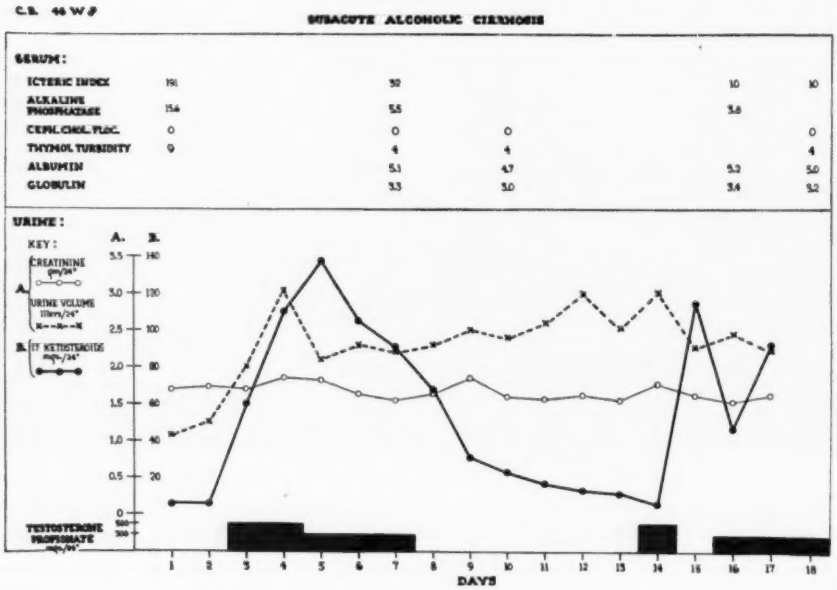
Physical examination showed a well-developed and nourished male deeply icteric and lethargic. Significant findings included: blood pressure 140/80; temperature 99.6°F.; pulse 86; rales at the bases of both lungs; and a smooth tender liver 6 inches below the right costal margin in the mid-clavicular line. Initial laboratory findings disclosed a leucocytosis of 12,250.

Total dose:—3.3 gm. (9 days).

Course:—Within 72 hours, following treatment a marked increase in appetite and sense of well-being was noted. A diuresis of 2,782 cml. of urine occurred in the initial 48 hours. A larger urine volume, ranging between 2,100-3,100 cml.

TABLE XV

BIOCHEMICAL DATA IN SUBACUTE ALCOHOLIC CIRRHOSIS
CASE 6 (C. B.)



as compared with control values of 1,250 cml., followed for the next 14 days. Fluid retention was not clinically detected at any time during treatment. A definite increase in libido was noted during the second week. Rapid decrease in liver size ensued and 16 days from onset of therapy the liver was palpable at the right costal margin.

Table XV presents the biochemical data.

Routine laboratory findings revealed a rapid drop in icterus; a return of elevated alkaline phosphatase and thymol turbidity values to normal. The serum albumin fraction was normal but the globulin fraction remained above 3.0 gm. Seventeen per cent conversion of the testosterone occurred and 6 days were

required after 1.9 gm. of testosterone propionate had been given, before the 17-ketosteroid level returned to the initial baseline. The creatinine excretion remained within the lower limits of normal and no "rebound" was noted after 1.9 gm. of testosterone was given.

Final evaluation:—Alcoholic intake was resumed upon discharge and approximately 6 months later a fourth re-entry was necessary. Peritoneoscopy was performed at this time and the gross histologic findings were consistent with subacute alcoholic cirrhosis. The microscopic section of the liver showed "cellular to fairly dense portal and perilobular fibrous tissue, graded 2 and 3 plus; marked disturbance of the normal architecture; fatty infiltration (3 plus); necrosis of liver cells 1 plus" (Ernest M. Hall, M.D.).

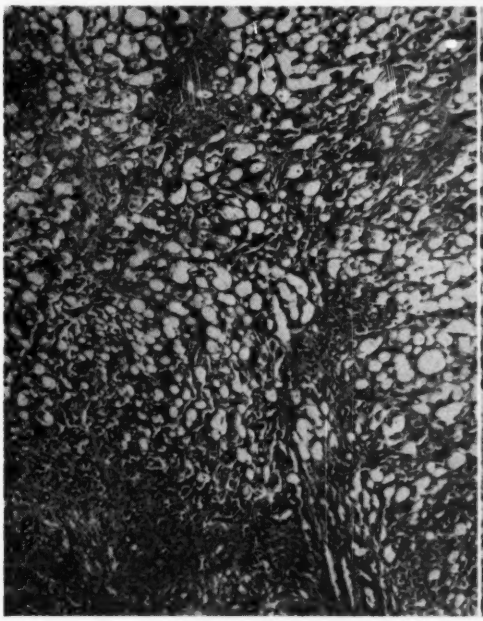


Fig. 3

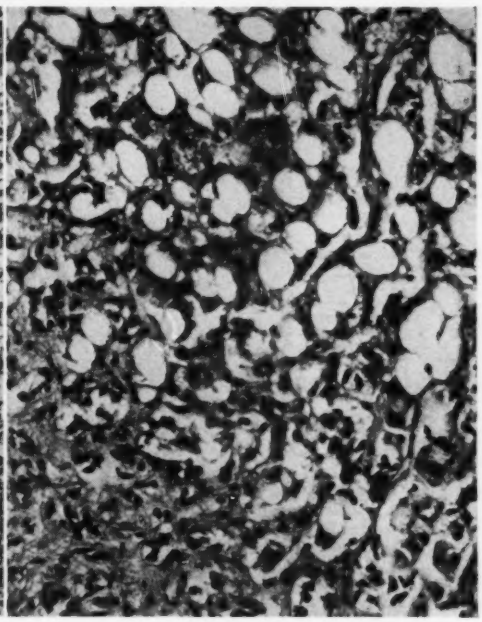


Fig. 4

Progressive hepatic coma with terminal hyponatremia; hyperpotassemia and uremia characterized the last three weeks before expiration.

Comment:—Rapid clinical and laboratory evidence of recovery, a persistently elevated globulin, diuresis with sustained increased urine volume, increased libido, intermediate conversion of testosterone to 17-ketosteroids, no significant variation in creatinine excretion after 1.9 gm. characterized this proven case of subacute alcoholic cirrhosis.

Case 7, Subacute Alcoholic Cirrhosis, Bronchopneumonia:—A white female (J. N.), aged 42, entered the hospital on March 13, 1951 complaining of dark urine, fever, sweats, and a productive cough for one week. The patient is a

known alcoholic and three previous records of pneumonia following heavy drinking of wine and whiskey are recorded. Her menstrual periods ceased 9 months ago.

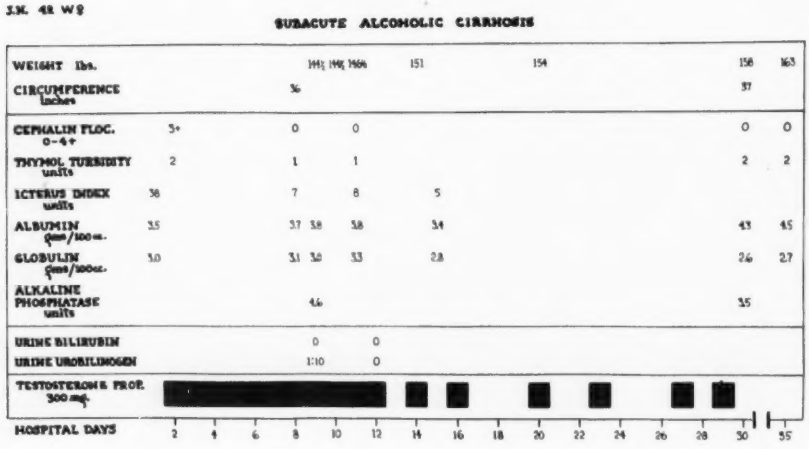
Physical examination revealed a disoriented, feverish, dehydrated and slightly jaundiced woman. Pertinent findings included; temperature 102°F, rales at the left lung base, a tender liver 6 inches below the right costal margin in the mid-clavicular line, and dry icteric skin with spider telangiectasia on the chest and neck. A leucocytosis of 20,600 with 97 per cent polymorphonuclear was present on admission.

Total dose:—5.2 gm. (20 days).

Course:—The patient received penicillin and 300 mg. of testosterone daily and within 4 days she was mentally clear, afebrile and eating. Her appetite

TABLE XVI

BIOCHEMICAL DATA IN SUBACUTE ALCOHOLIC CIRRHOSIS
CASE 7 (J. N.)



became ravenous during the next 3 weeks and she gained 27 pounds with no clinical evidence of edema. Her abdominal circumference was 36 inches on admission and 1 month later was 37 inches. A marked increase in libido developed at the end of the second week. During the third through sixth week testosterone was given twice weekly. After each injection an acne-like eruption developed on the face and chest. These eruptions ceased when testosterone was discontinued. The liver was 1 inch below the right costal margin on discharge.

The laboratory data show the following: a normal icterus, reversion of 3 plus cephalin cholesterol flocculation to negative by the 15th day after the onset of jaundice. The serum albumin remained low (3.4 gm.) and the globulin elevated (above 3.0 gm.) during the first 2 weeks, although a weight gain of 7 pounds

occurred. Two weeks later the serum albumin was within the normal range 4.5 gm. and the globulin an equivocal 2.7 gm.

Final evaluation:—Five months later revealed continued clinical progress with an additional 5 pounds in weight. The liver was palpable at the costal margin and there was no edema.

Comment:—Salient features include: rapid resolution of bronchopneumonia and mental disorientation, marked gain of weight, increased libido, development of acne, and return of the albumin/globulin determinations to normal.

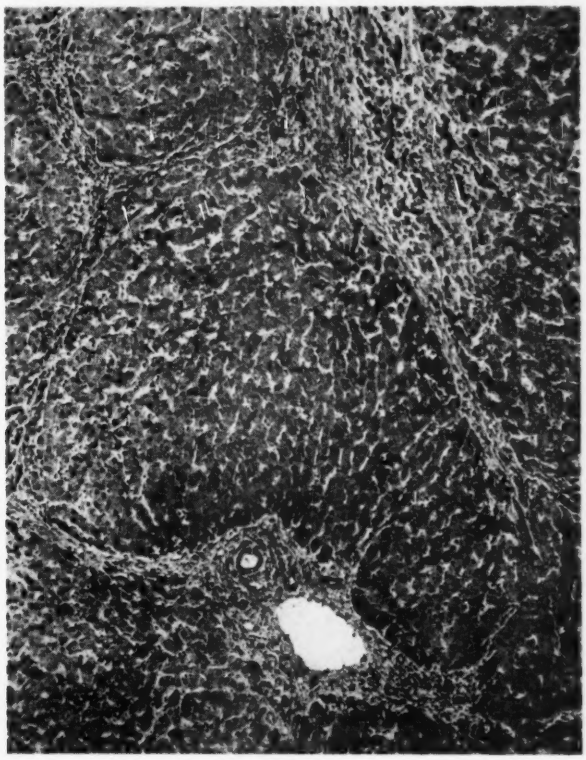


Fig. 5

Portal Cirrhosis

Case 8, Atrophic Portal Cirrhosis:—A white male (T. B.), 49 years old, with known cirrhosis of the liver, was readmitted on March 19, 1951 complaining of anorexia, a weight loss of 20 pounds, jaundice, ascites and edema for 2 months. Four paracenteses had been performed within a period of 3 months.

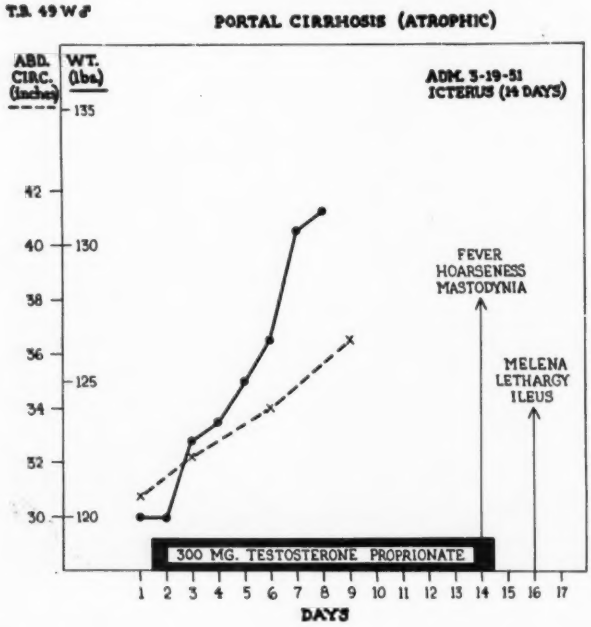
Physical examination disclosed a chronically ill and jaundiced patient. Further findings were rales at the base of the right lung, moderate ascites, a firm tender liver palpable 3 cm. below the right costal margin, ankle edema, and spider telangiectasia.

Total dose:—3.9 gm. (300 gm. 13 days).

Course:—Testosterone was administered the day following entry, and a progressive increase in anorexia and fluid retention developed as is schematically outlined by Table XVII. The gain of 11 pounds in weight, increase in abdominal girth by 4 inches during the first week is graphically shown. Mercuhydrin 2 c.c. (i.m.) was given on the 7th, 10th and 12th days. Marked hoarseness of voice, painful tender breasts, and a fever of 102°F appeared on the 14th day. Although testosterone administration was stopped, lethargy, melena and an ileus subsequently ensued. Chemical determinations at this time revealed hyponatremia, metabolic acidosis, elevation of the nonprotein nitrogen, and a normal serum

TABLE XVII

SCHEMATIC REPRESENTATION OF CHANGES IN PORTAL CIRRHOSIS
CASE 8 (T. B.)



potassium. Exact values were: serum sodium 311 mg. per cent (320-370), carbon dioxide combining power 41 volumes per cent (55-70), NPN 81 mg. per cent (25-39), serum potassium 17 mg. per cent (16-22). Flat plate of the abdomen demonstrated gaseous distention of the stomach and small intestines and considerable intra- and extraluminal fluid.

Gastrointestinal suction, intravenous glucose, and antibiotics produced a gradual improvement. The mastodynia, fever and lethargy cleared within 4 days. One week later the patient left the hospital without consent. He reentered 12 days later following a massive hematemesis and expired the following day.

Final evaluation:—Autopsy disclosed a typical small cirrhotic liver with bleeding secondary to varices in the cardia of the stomach.

Comment:—Several observations are noteworthy: First, the marked fluid retention in portal cirrhosis following the use of large doses of testosterone was not controlled by mercurial diuretics or sodium restriction; Second, end organ responses without libido may develop in certain cases of portal cirrhosis if sufficiently large doses of testosterone are given.

Case 9, Portal Cirrhosis, Compensated Hypertensive Heart Disease:—A white female (G. G.), aged 46, entered the hospital May 15, 1951 because of nose bleeds and vomiting. There had been many previous admissions for treatment of cirrhosis.

TABLE XVIII

BIOCHEMICAL CHANGES IN PORTAL CIRRHOSIS WITHOUT INCREASED FLUID
CASE 9 (G. G.)

G.G. 46 W ♀ ADM. 5-15-51 — PORTAL CIRRHOSIS

SERUM:												
ICTERUS INDEX	12	12			8				8			
ALKALINE PHOSPHATASE	8.5				5.3				4.2			
CEPH. CHOL. FLOC.	4+	2+	1+		3+				1+			
THYMOL TURBIDITY	4	1	4		4				1			
ALBUMIN	3.1	3.1	3.0		3.1				3.4			
GLOBULIN	3.9	3.3	3.1		3.6				3.7			
WEIGHT (lbs.)					139	140	140	142	139	139		
URINE:												
VOLUME (24°)					1400	1400	1300	1350	1000	1050		
SODIUM												
MGMS.					150	160	170	170	190	120		
GMS.					2.1	2.3	2.2	2.3	1.9	1.3		
POTASSIUM												
MGMS.					240	270	272	271	271	220		
GMS.					.34	.38	.35	.37	.27	.23		
CHLORIDE												
MGMS.						430	440	400	420	280		
GMS.						6.0	5.7	5.4	4.2	3.0		
TESTOSTERONE PROPIONATE 300mgms./day												
	4	6	8	10	12	14	16	18	20	22	24	26	28

Physical examination showed an obese, shaking, and disoriented woman whose sclerae were icteric, heart was enlarged, blood pressure 200/110, and pulse 96. The liver was palpated 3 inches below the right costal margin in the mid-clavicular line.

The laboratory tests on admission were as follows: icteric index 12, alkaline phosphatase 8.5, cephalin cholesterol flocculation 4 plus, thymol turbidity 4, and albumin/globulin 3.1/3.9.

Total dose:—5.7 gm. (19 days).

Course:—The patient improved mentally and noted a mild improvement in appetite. In the absence of salt restriction no clinical edema or ascites developed. The biochemical changes are shown in Table XVIII.

The icterus decreased from 12 to 8; the alkaline phosphatase dropped from 8.5 to 4.2; the cephalin cholesterol flocculation decreased from 4 plus to 1 plus within 10 days and subsequently varied from 3 to 1 plus; the albumin/globulin ratio remained essentially unchanged; a consistently low urinary potassium excretion was noted in spite of an adequate diet.

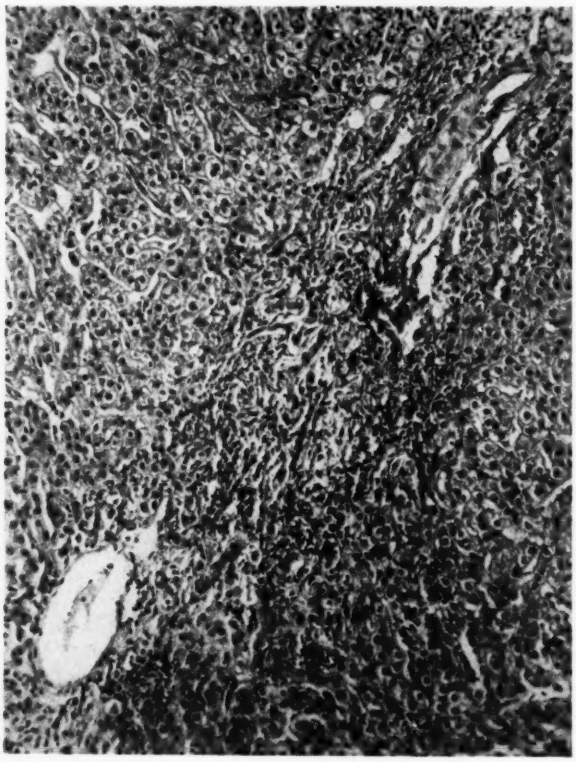


Fig. 6

Comment:—Salient features of this unusual patient were: absence of secondary hormonal manifestations and fluid retention after a large total dose of testosterone, and marked renal retention of potassium.

Xanthomatous Biliary Cirrhosis

Case 10, Hepatocellular Hypercholesterolemic Cirrhosis:—A white female (F. H.), 56 years old, noted an insidious onset of pruritus, jaundice, dark urine, clay colored stools, profound anorexia, fatigue and a 70 pound weight loss during the 6 months prior to admission on May 18, 1951. There was no history of pre-

vious episodes of pain, or injections of any nature. She was known to have hypertension with anginal episodes.

Physical examination showed her emaciated, jaundiced and moderately ill. Significant findings were blood pressure 140/80, pulse 92, temperature 98.6°F, a grade two apical systolic murmur, rales at both lung bases, a firm tender liver 2 inches below the right costal margin in the mid-clavicular line, and a palpable spleen.

Total dose:—4.2 gm. (14 days).

Course:—Clinical deterioration with anorexia, apathy and persistent hepatosplenomegaly followed a standard cirrhotic regimen for 3 weeks. A clear serum showed elevated cholesterol, phospholipid, and alkaline phosphatase values and subsequently transient cutaneous xanthomata appeared on the creases of the palms, elbows and eyelids. Peritoneoscopy was performed on May 23, 1951, and

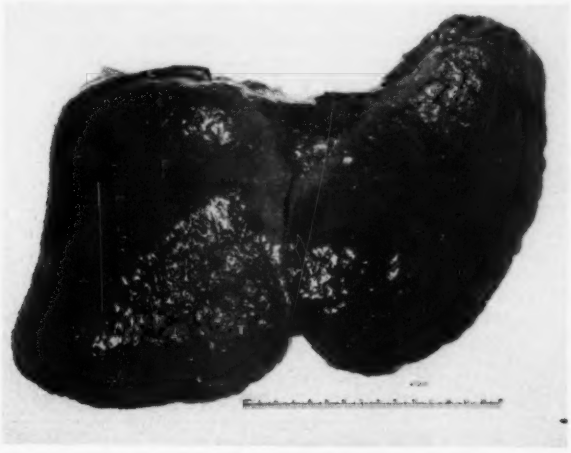


Fig. 7—Gross appearance of liver in Case 10 (F. H.)

the liver was described as "larger than normal, the surface coarsely granular with some lobulation; numerous white cysts (probably inflammatory) were seen; on biopsy the liver substance appeared edematous". The microscopic diagnosis of the liver biopsy was "subacute stage of atrophic cirrhosis".

Within 3 days after treatment improvement in appetite and sense of well-being was noted. On discharge 2 weeks later the spleen was not felt and the liver was palpated at the right costal margin.

The pre-treatment total cholesterol value of 560 mg. per cent was reduced to 460 mg. per cent; the phospholipid fraction increased from 32.7 mg. per cent to 40 mg. per cent; the fasting chlomicron count which averaged 65 per cent was reduced to 37 per cent after the administration of 4.2 gm. of testosterone. The decrease in the chylomicron count appeared to correlate with the increased phospho-

lipid level and the increased phospholipid cholesterol ratio of 2.1[1]. Twenty-four days after treatment the serum cholesterol was 4.7 mg. per cent, however, the lipid phosphorus was reduced to 31 mg. per cent and the chylomicron count increased to 57 per cent.

Note the initial diuresis 72 hours after testosterone therapy; the progressive rise in urinary sodium and chloride concentration and excretion; the potassium retention until the 11th day of treatment when both the urinary concentration and the total amount of this ion increased.

Clinical improvement continued while discharged and the patient performed her own house work and ate well. Twelve days after discharge on routine treat-

TABLE XIX

BIOCHEMICAL DATA IN XANTHOMATOUS BILIARY CIRRHOSIS
CASE 10 (F. H.)

F.H. 56 W ♀

XANTHOMATOUS BILIARY CIRRHOSIS

CHYLOMYCRON %			65			57	34				37					57		67	
CHOLESTEROL (Total)			560								460					417		67	
PHOSPHOLIPID			32.7								40					31			
RATIO PHOSPHOLIPID / CHOLESTEROL			1.46								2.1					1.9			
URINE:																			
SODIUM																			
MG. %	130	140	160	111	140	140	130	230	170	143	155	160	203	164					
GMS. TOTAL	1.2	1.4	2.0	0.8	3.2		1.7	2.0	1.5	1.0		2.4	2.8	1.9					
POTASSIUM																			
MG. %	300	340	260	240	210	300	220	420	350	250	430	740	1170	1010					
GMS. TOTAL	0.3	0.3	0.3	0.17	0.48		0.29	0.38	0.32	0.35		1.1	1.6	1.2					
CHLORIDE																			
MG. %	350	380	475	300	340	360	338	630	440	220	520	360	560	420					
GMS. TOTAL	3.1	4.0	5.2	2.1	7.8		4.4	5.7	3.9	3.7		5.4	7.7	5.0					
URINE VOLUME cc.	900	1025	1275	700	2300	1300	900	900	1400			1500	1240	1200					
WEIGHT LBS.	101		100	101	98	101¾	101		100			99½		98					
TEST. PROPIONATE						4.1 GMS.													
DAYS AFTER HOSPITALIZATION	22	24	26	28	30	32	34	36	38	40		58		68					

ment the serum albumin was 4.2 gm.; the serum globulin 2.7 gm. as compared with values of 2.2 gm. of albumin and 5.7 gm. globulin 4 days after discharge. Twenty-four days later a weight gain of 8 pounds occurred and cutaneous xanthomata appeared on the hands, elbows and eyelids. At this time the lipid studies showed a reversion to near pre-treatment values. A gradual decrease in appetite and physical strength began approximately one month after treatment and hospitalization was necessary after a temporary remission of 80 days on September 9, 1951.

A total of 4.1 gm. of testosterone was given over an 11 day period with a less prominent clinical response. After a total of 2.6 gm. of testosterone the A/G

ratio changed from 3.8/5.6 to 4.5/2.0. Two weeks later, however, values of 3.9/5.4 were obtained.

The patient expired July 13, 1953. Autopsy findings were consistent with xanthomatous biliary cirrhosis (Hugh Edmondson, M.D.).

Comment:—Significant observations were as follows: temporary clinical remission, increased phospholipid level coincident with lowering of the chylomicron count, diuresis, absence of salt and water retention, initial potassium retention, and temporary changes of the albumin/globulin ratio toward normal following treatment.

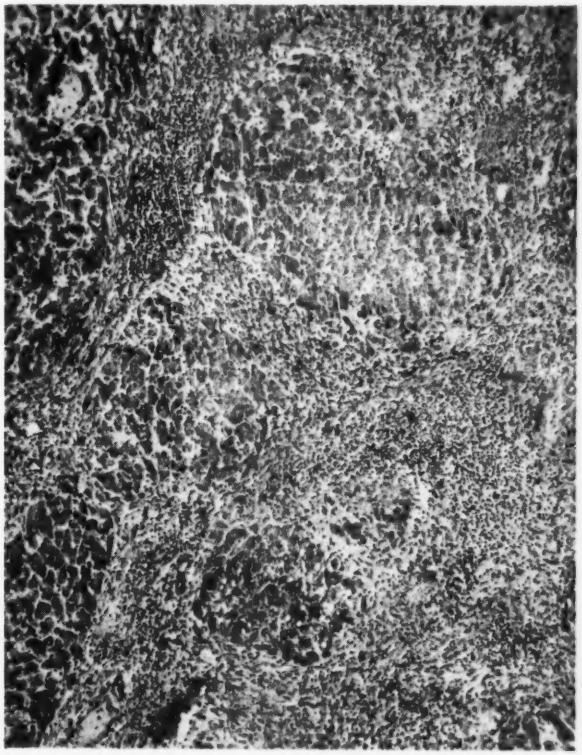


Fig. 8—Histologic appearance of liver in Case 10 (F.H.).

Discussion

The anabolic and glycogenic effects of testosterone propionate in experimental animals, eunuchs and normal men are well substantiated by an increased muscle mass, and by retention of nitrogen, potassium, phosphorus and water[8,10,11a,b,c,12,a,b,c,13,16,19,20]. Although the exact mechanism of this action is unknown, partial inhibition of pituitary hormone excretion with the development

of a relative adrenalcortical insufficiency upon discontinuing testosterone has been reported[2,6,7].

Since reparation of a liver depleted of protein and glycogen is dependent upon reaching and maintaining a positive nitrogen balance, testosterone has been used in a preventative and therapeutic role. The average daily dose has varied from 25 to 100 mg.[16,17]. Histological improvement in subacute alcoholic cirrhosis has been correlated with the attainment of a positive nitrogen balance[3,6]. Recent investigations found this hormone effective in preventing postoperative hepatic dysfunction and in producing net gains in body protein and in liver glycogen[11]. Testosterone is the only agent capable of reversing the increased catabolism of sulfur containing amino acids and the negative nitrogen balance found in chronic viral hepatitis[11d].

Many of the clinical responses observed in the 43 cases of liver disease studied in this report are related to the known protein anabolic and glycogenic effects of this steroid. Objective anabolic manifestations include the following: (1) Significant weight gains during and after treatment in most patients with hepatitis and alcoholic cirrhosis; (2) selective urinary potassium retention (cases G. G. and F. H.), (3) progressive increases in serum albumin levels in potentially reversible liver disease. Glycogen storage is indicated by the improvement in glucose and cholesterol metabolism observed in acute hepatitis complicated by diabetes mellitus (M. M.)[10].

Important factors affecting the individual response include the nature and potential reversibility of the pathological process, variations in fluid retention, concurrent diseases, and dose and total quantity of testosterone administered.

Potential antianabolic activity after prolonged use of this steroid is suggested by the data obtained from two patients with acute hepatitis. A weight loss of 5 pounds, and an abnormally high creatinine excretion followed the injection of 4 gm. in L. L. J. B. gained approximately 10 pounds after 3.9 gm. of testosterone in 13 days. Stabilization of weight occurred, however, when an additional 2.4 gm. was given. A rapid gain of 5 pounds within 4 days followed the cessation of treatment.

Kochakian observed concommitant loss of nitrogen retaining ability and of body weight with extension of testosterone injection in rats[12c].

The data obtained from this preliminary study is statistically inadequate to indicate alteration in the course of patients with acute hepatitis or subacute alcoholic cirrhosis. The clinical observations in these patients, however, may have practical therapeutic application. Rapid and striking improvement may be obtained in those cases of acute hepatitis with symptoms of severe anorexia and mental apathy who are treated soon after the onset of jaundice. Testosterone appeared capable of improving appetite and sense of well-being during all phases of this disease. A similar response may be anticipated in subacute alcoholic

cirrhosis. The deteriorating course of A. G. with subacute alcoholic cirrhosis was altered by testosterone after the development of a resistant bronchopneumonia. The resurgence of host-resistance to infection as well as the restoration of appetite demonstrated by this case was observed to a lesser degree in the 4 other patients of this group. An additive or synergistic action with antibiotics is suggested by this response.

Most patients with portal cirrhosis responded poorly to the daily administration of 300 to 500 mg. of testosterone. The increased fluid retention thereby induced in an irreversibly damaged liver appeared to determine the clinical response. Temporary improvement was noted in those cirrhotic patients in which fluid retention could be partially controlled[16]. Clinical and electrolyte studies disclosed the absence of excessive sodium or water retention in only one case of portal cirrhosis (G. G.)[19]. In general, large doses of testosterone propionate appear contraindicated in the majority of patients with decompensated portal cirrhosis. Several temporary remissions followed treatment in one case of xanthomatous biliary cirrhosis. One case of posthepatitis cirrhosis with hypothyroidism lost weight and improved clinically following concurrent testosterone and thyroid therapy.

17-Ketosteroids

Experimental and clinical data has implicated the liver as the primary site for the conversion of testosterone propionate to 17-ketosteroids[4,9,12,13,17].

The use of 1,000 mg. of this hormone as a stress dose disclosed a comparative decrease in the conversion capacities of cirrhosis in contrast to hepatitis. The fact that none of the ten portal cirrhotics were able to convert more than 10 per cent of the injected dose is pertinent. Complicating diseases lowered the rate of conversion of patients with acute hepatitis.

Normal control values utilizing this "testosterone tolerance test" were not obtained. West found a reduced rate of conversion in cirrhotics as compared with normals following an intravenous tolerance test[19,20]. The mean conversion rate in 24 normal men was 35 per cent as compared to 22.5 per cent in 6 patients with liver disease (5 portal cirrhotics and 1 serum hepatitis) when 50 mg. was used as the test dose. The range in normal men varied widely and the patients with liver disease in this series fell within the lower limits of normal[5]. It is noteworthy that the 17 patients given the 1,000 mg. tolerance test were subjected to 20 times the stress dose used in the above investigation.

Further confirmation that the urinary 17-ketosteroids do not necessarily represent the hormone involved in the anabolic process is found in this study. Normal 17-ketosteroid values were found in an acute hepatitis patient with progressive end organ response (Case 3—H. C.). An inverse relationship between 17-ketosteroid excretion and anabolism is shown in C. B. with subacute alcoholic

cirrhosis. Prior investigations have indicated that maximal anabolic activity as measured by nitrogen retention is dependent upon fixation of the hormone in the tissues by means of high doses, and that the 17-ketosteroids largely represented excess circulating hormones plus a small amount derived from intracellular turnover in target organs[19,20].

Creatinine

The twenty-four hour creatinine excretion was consistently higher in patients with hepatitis as compared to the portal cirrhotic patient. Creatinine coefficients and total excretions were abnormally elevated in three hepatitis patients who had received more than 4 gm. of the hormone. An interesting observation was the prompt decrease in these values toward the normal range following the readministration of 1,000 mg. of testosterone propionate. Extremely low control creatinine excretions and coefficients were found in four patients with cirrhosis. These values were further depressed by the administration of testosterone.

Since creatinine is derived directly from creatine, the following inferences are suggested by the above observations[3]. (1) An increased creatine to creatinine conversion with subsequent increased creatinine excretion may follow administration of large doses of testosterone in acute hepatitis. The "rebound toward normal" of the high creatinine excretion observed following retreatment may indicate further creatine storage. (2) The fact that creatinine excretion varied but slightly in one case of subacute alcoholic cirrhosis may be related to the small total dose administered (1.9 gm.). (3) The extremely low creatinine excretion and creatinine coefficients in cirrhotics may indicate impairment of creatine synthesis due to the severe liver damage.

Secondarily Induced Changes

An increased libido in both sexes became apparent during the convalescent phase of most cases of acute hepatitis and subacute alcoholic cirrhosis. No such change developed in the far advanced cirrhotics. End organ responses (masculinization of voice, hirsutism, acne, mastodynia) were detected only in those women who received more than 2 gm. of testosterone. The cirrhotic patient with several exceptions demonstrated none of these findings.

Severable possible conclusions are suggested by this data. First, the return of adequate liver function is apparently necessary for libido as well as the appearance of end-organ changes during the convalescent phase of potentially reversible liver disease. Second, the initial catabolic phase of acute hepatitis and subacute alcoholic cirrhosis appears to suppress the appearance of these changes. Third, the development of secondary hormonal changes seems governed by the total dose as well as by the inherited patterns of the end-organ. Fourth, exogenously induced changes once present may persist and in certain cases

progress in the absence of any further stimulus. Fifth, the absence of end-organ response in most cirrhotics may in part result from the early discontinuance of treatment because of fluid retention.

Summary

1. In a study of 44 cases of acute and chronic liver disease, high doses of testosterone propionate appeared capable of improving appetite and sense of well-being during all phases of acute hepatitis and subacute alcoholic cirrhosis. Marked benefit was obtained by the daily administration of 300 mg. of testosterone during a three to five day period to those anorexic, depressed or secondarily infected patients. Statistically, however, no alteration in the clinical course of these diseases could be established by this investigation.

2. Control of fluid retention is a prime factor governing the clinical response in portal cirrhosis. In general, the use of large doses of testosterone in cirrhotics is contraindicated because of increased ascites and edema, although improvement may occur in some cases.

3. The appearance of secondary hormonal changes during the convalescent phase of acute hepatitis and subacute alcoholic cirrhosis correlates with the return of adequate liver function. An increased libido developed in both men and women of this group. Untoward androgenic effects occurred solely in those women in whom the total dose exceeded 2 gm. The cirrhotic was usually characterized by the absence of both subjective libidinous and end organ changes.

4. A significant reduction was observed in creatinine excretion and in the rate of conversion of testosterone to 17-ketosteroids in portal cirrhosis as compared with acute hepatitis.

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DUODENAL STASIS CAUSED BY AN ABERRANT SUPERIOR MESENTERIC VESSEL*

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Sixty years ago in the Presse Medical of Paris, Glenard's[1] classical study of enteroptosis was published. It attracted considerable attention and led to all sorts of high calorie diets plus abdominal belts, and in addition, to many operations for shortening or plication of mesenteries and omenti. As is the historical custom of medical discoveries extremes creep in and it wasn't long before even total colectomies were being advocated as the only cure for this state of enteroptosis. The diagnosis became a very fashionable one and was the vogue of its day and presumably was the topic of discussion at the teas and soirees of the time, bridge and canasta not yet having been born.

As is usual with medical vogues, it is as in a play, the star occupying the center of the stage, flood lighted to the nth degree, then slowly the lights dim, the stage becomes dark, the star retreats into the wings and the show is over. So it was with Glenard's disease or enteroptosis—hardly anybody speaks of it today.

In passing, however, Glenard mentioned that in his studies he had come across cases of dilatation of the second and third portions of the duodenum caused by constriction by an aberrant branch of the superior mesenteric artery in such manner that a definite partial obstruction of varying degree followed. It is with this duodenal stasis caused by constriction by either the superior mesenteric artery itself or an aberrant branch that is the substance of this study.

It is all the more trite that Glenard's studies be mentioned at this time because that part related to the duodenal stasis and dilatation attracted very little attention. The idea was developed no further by him and automatically his description fell by the wayside.

In his report he called attention to the pull of the ptosed intestine in this area, causing such tension that the mesenteric vessel became like an elastic band, stretched tight and acting as a constricting cord across the duodenum. That particular type of syndrome is mentioned in passing but is not included in the subject matter of this paper.

Glenard's attention and enthusiasm being devoted entirely to his newly discovered ptosis, he described changed arterial relationships as only of minor

*Read before the Eighteenth Annual Convention of the National Gastroenterological Association, Los Angeles, Calif., 12, 13, 14 October 1953.

influence. The observation of the possibility of the same syndrome occurring in people who had increased their weight to an exaggerated degree apparently escaped his attention as his report constantly refers to the asthenic woman who has lost weight.

That the symptoms produced by duodenal compression have caused considerable mental perturbation in the minds of notably keen students of medicine is evidenced by the fact that such names as Ochsner[2], Finney[3], Bloodgood[4], and Barker[5] are met with in association with the literature pertaining to the disorders of this region.

About twenty years after Glenard, in 1907, Stavely[6], at Johns Hopkins Hospital, called attention to certain symptoms which followed gastroduodenostomies, and after some detailed studies, called attention to the intermittent duodenal obstruction accompanied by chronic duodenal stasis produced primarily by mesenteric artery compression. Since then other investigators have studied and elaborated on his description.

Pause should be in order here to pay tribute to Stavely, because almost half a century later the operation which he proposed and carried out at that time is the operation of choice today.

Attempts at more minute and sharply focalized diagnosis in the field of gastroenterology often meet with the criticism that the addition of new terms to the existing nomenclature, plus the addition of symptoms described as a group under the heading of syndromes, serves only to confuse. That such a criticism is hardly fair is obvious. The better we as physicians understand how a symptom or a group of symptoms is produced, the better we are able to spot or pinpoint our diagnosis, the better we shall be able to guide and treat patients rationally and successfully.

Specifically, the group of patients composing this study presented a train of symptoms which from the history and physical examination suggested almost invariably the presence of duodenal pathology. The first case seen was in consultation with a medical student in an out-patient clinic. His keen eye had picked up visible reverse or antiperistaltic waves rippling upward for about six inches from a point about an inch below and to the right of the umbilicus. With the enthusiasm of youth, he wanted to know why and so detailed study of the duodenum and jejunum was done, fluoroscopically and roentgenologically, and the diagnosis made of duodenal stasis caused by constriction of the third portion of the duodenum, presumably by an aberrant branch of the superior mesenteric artery. With almost incredible luck, this patient was operated on four to six months later for a ruptured tubal pregnancy and the duodenal diagnosis corroborated by direct visual inspection of the area.

Approximately a month or two later a similar case presenting visible antiperistaltic waves in the same area—just below and to the right of the duodenum

—was seen. Again incredible luck and some months later the patient was operated on for an acute abdominal emergency and the internes and residents were able to verify the diagnosis by direct visual inspection of the area.

Then over a period of about twenty years, wherein about twenty-five cases were seen, which is an indication of the relative frequency of this syndrome—in not a single case except those first two have we seen visible antiperistaltic waves in the duodenal area on the abdomen.

Unfortunately examination of the duodenum by many roentgenologists is entirely too casual and is limited to whether or not an ulcer is present. There exist many roentgenologists who do not, or will not concede that there exists such a syndrome as duodenitis. If duodenal irritability and inconstant irregularity are grossly evident, a certain percentage of keener-minded or possibly better trained and experienced roentgenologists will venture, sometimes with trepidation, a diagnosis of duodenitis.

When one is presented with a patient in whom there is a definite complaint referable to the duodenum, and the presence of ulcer has been ruled out, it is almost compulsory that one should search more intensely and minutely other parts of the duodenum than the bulb for an adequate explanation as to how the symptoms have been produced.

In speaking of the duodenal type of symptoms, reference is made to epigastric pain and burning, occurring two to three hours after food intake, eructation of hyperacid fluid or food, vomiting of hyperacid gastric content, fullness and distention in the mid-epigastrium accompanied by burping or belching of gas, or in other words, symptoms similar to those in cases of the true ulcer.

As mentioned above, too frequently examination of duodenum, particularly fluoroscopically, is confined to little more than a view of the bulb with little or no attention paid to the second and third portion of that structure.

In cases such as those mentioned, further study of the outline and structure of the duodenum, particularly of the second and third portions is indicated, and in addition possibly studies as to function. Intubation and suction of duodenal content for study can be of help in corroboration.

Clinically what impresses one most in these cases is that in a large percentage, certain associated gross body changes, particularly with regard to marked alteration in body weight, are common. Following the first two cases cited in this paper as having visible abdominal antiperistaltic waves an unusual opportunity presented itself to study a group of women who had been following drastic reducing schedules, but under supervision of a competent physician. Several of these women who had never experienced any gastrointestinal distress of any kind previously, found themselves having symptoms of duodenal disorder.

The common factor in all was that marked changes had taken place in the body contour and secondarily that just as marked changes must have taken place in the internal body mechanics as the results of alteration of anatomic relationships, each patient had begun to complain of duodenal type of symptoms shortly after the weight change had taken place. Conversely, as the study of such cases was elaborated, the addition to the series of many in whom gross and excessive addition of weight had occurred became necessary, as in these cases, there was present the identical factor common to all, namely, alteration in anatomic relationship. This alteration was confined to a specific area, namely, that wherein the superior mesenteric artery or an aberrant branch lay in contact with the duodenum or crossed it, usually in its third portion.

Roentgenologic examination of these patients showed the bulbous area invariably negative for ulcer, so attention became automatically focussed on the second and third portion of the duodenum, more on the latter.

In the beginning of the studies it was somewhat astonishing to discover a more than seeming percentage of cases in which anomalous position of either the superior mesenteric vessel itself or an aberrant branch crossing the duodenum produced, first, duodenal compression; second, duodenal stasis and, third, duodenal obstruction, partial, intermittent or even complete. We have just seen a case in which the obstruction was to all intents and purposes complete.

This observation of the part played by an aberrant branch of the superior mesenteric vessel we were able to corroborate in several instances through the intermediary of a series of fortuitous occurrences, fortuitous let us say from the standpoint of us who were doing the studying.

One of the young women in this series developed a ruptured ovarian cyst. Operation presented no particular difficulties, so advantage was taken of this to explore the area of the duodenum, more particularly the region of the superior mesenteric artery. As suspected, an aberrant branch of the artery was located, crossing the third or terminal portion of duodenum in such a manner as to act as a constricting band.

A short while later a similar opportunity presented itself where the primary surgery was in another part of the abdomen. Exploration revealed pathologic features identical with those in the above mentioned case, except perhaps for a slight divergence in the direction of the crossing of the aberrant branch, it being a bit more oblique than transverse.

Later, under somewhat similar circumstance, a case was encountered in which compression of the duodenum, with attendant stasis and duodenitis, was caused by the compression of the superior mesenteric vessel itself.

It is reasonable to presume, therefore, in view of the number of cases clinically presenting this syndrome, that an anatomic alteration of the kind

just described, particularly one in which an aberrant branch is encountered, may be more frequent than is suspected. In spite, however, of the compressing position of the artery, or its branch, no symptoms had been complained of in the cases studied, therefore, in all probability no duodenal tissue changes had taken place until marked alterations in the body structure itself had occurred through either gross depletion or gross additions of fat to the body. We would like to emphasize this statement because in a recent round table discussion of the subject perhaps inadvertently we stressed entirely too much the surgical approach to the problem and internists challenged rightfully that the solution of the problem was not entirely surgical and that they had helped many cases by nonsurgical procedures. We agree entirely with the internists contention. Incidentally, we were agreeably surprised at the number of men present at this conference who later approached us and told us that they were totally unfamiliar with such a diagnostic concept and would watch for it from then on.

It would perhaps be best to state here that the syndrome herein described should not be confused with other causes of duodenal stasis, such as:

a. Gastroptosis or enteroptosis
b. Congenital anomalies involving length of mesentery
c. Congenital bands
d. Extrinsic pressure on duodenum by periduodenal inflamed or enlarged glands
e. Periduodenal inflammation
f. Benign or malignant tumors or cysts
g. Aneurism of abdominal aorta

Etiology

The changes in mechanical relationship and proximity of the structures in the second and third portions of the duodenum to those surrounding them become grossly distorted when tissue changes take place. In the process of dieting to reduce weight, as an illustration, particularly if the weight reduction is drastic, one is aware of the fact that the intra-abdominal mesenteries and the omenti, plus the retroperitoneal spaces, lose fat in quantity and early in the process prior even to the external structures of the body. Particularly is this true of such structures as the hepatoduodenal ligament, the gastroduodenal ligament, the gastrocolic ligament and the lesser and greater omenti. This is readily verified whenever exploratory laparotomy is done in cases in which advanced or even moderately advanced gastrointestinal malignancy or any other wasting disease is present. In the process of adding on a great deal of weight, it is in these same structures, mesenteries, abdominal ligaments, omenti and retroperitoneal spaces, that fat is deposited in proportional amount, filling them out in about the same way in which a pillow is stuffed, thereby changing anatomical lines and creating angles and stresses and even distortions.

The basis anatomy of this syndrome is that when the third or fourth portions of the duodenum, or both pass high in the abdomen to cross the aorta, the bowel is fixed immediately adjacent to the superior mesenteric artery, establishing a focal area highly susceptible to pressure pull and stress.

Position of the body may influence the degree and time of symptoms. One can theorize that aggravation of symptoms should occur on standing, be somewhat ameliorated on lying down and disappear completely if the position of a quadruped were assumed.

Symptomatology

Just what are the symptoms of this syndrome? They very definitely are varied. Perhaps it would be best to list them in the order of their relative frequency.

1. Mid-epigastric discomfort:—This is truly a discomfort—rarely does it reach the status of a pain. Food intake increases the discomfort usually wherein in taking the history it differs from an ulcer story where pain relief on food intake is the usual. Hyperperistalsis proximal to the obstructive line can be of a degree to cause soreness even spasm and rigidity of the overlying musculature.

2. Bloating and Flatulency:—This is indeed present in every case. It is probably due to fermentation of both gastric and duodenal content particularly in the trapped food content proximal to the constriction. Often aggravating this symptom may be a reflex disturbance in a practically adjacent gallbladder.

3. Vomiting:—Another symptom present in every case occurs without nausea, probably mechanical, and is the stomach's mode of getting rid of something which is offending. It is invariably copious and symptomatic relief is obtained as soon as the stomach is empty. Dehydration and loss of chlorides, frequently complicate the picture, producing acidosis, with increased vomiting dehydration and dechlorination, so that a vicious cycle is set up. A minor but important detail is the presence of far more than the ordinary content of bile in the vomitus.

4. Constipation:—This is the rule and is secondary to lowered food intake on the part of the patient because of fear of ensuing symptoms and because of disturbed digestion in the small intestine.

5. Headache, dizziness, vertigo:—These may be due to the absorption of toxic products through the duodenal wall into the general circulation, inspiring some who have described this syndrome to coin the term, "Duodenal Migraine".

6. Epigastric burning:—This occurs less frequently than any of the other symptoms. It may perhaps be due to the back pressure exerted against the pyloric ring by the reverse peristalsis, allowing a gush of concentrated acid into the duodenum overcoming the neutralization of the normal duodenal content.

Objective Signs

If an associated endocrine, metabolic or deficiency state is present as an underlying factor, it can often be noted on inspection of the patient while taking the history, as the degree of such change is likely to be marked in these cases.

Mild disturbances in these conditions do not produce sufficient tissue change to alter the mechanical relationship necessary to produce the symptoms of this syndrome. The condition of the serious hyperthyroid individual is usually obvious from mere casual observation. The same is true of the hypothyroid, hypo-ovarian, myasthenic or anemic, etc., patient. Invariably if any of these states are underlying factors, they are so grossly evident as to be quite obvious.

Among the patients in whom none of these changes is underlying, one is confronted most frequently with women who have undergone drastic dietary restriction for the purpose of weight reduction.

The objective signs are confined to the abdomen alone, except in cases in which signs of the associated syndromes are present in addition. These signs are tenderness and spasm of the upper abdomen, confined mainly to the epigastric and periumbilical areas. With a slight stretch of the imagination one could say that perhaps the localized point or area of acute tenderness is not as sharply defined or focal as in a case of duodenal ulcer. Oftentime symptoms occur intermittently in mild attacks, and because of their similarity to attacks of gallbladder disease and the presence of quantities of bile in the vomitus, they are described by the patient as "bilious spells".

Laboratory Procedures

These do not give much help. Gastric analysis returns no usable information and neither does duodenal intubation with secretion study. Except for disclosing an anemia, if present, no help can be had from a complete blood examination.

The same can be said for the basal metabolism. It is wise to do one sort of routinely but unless a real low rate comes to light it contributes nothing.

Roentgen Examination

Here it is different. We do get help. X-ray is of the utmost value in the diagnosis of this syndrome and particularly, stress is laid on the fluoroscopic examination of the duodenum. The stomach and duodenum being found negative for ulcer, routine examination of the gallbladder is essential in order that any pathologic change here may be excluded.

The absence of stone, although not entirely conclusive from roentgenographic examination, when coupled with the absence of inflammatory change in the gallbladder and its motility and dye-absorptive and excretive power normal,

indicates that more searching examination of the duodenum is in order. All too frequently the second and third portions of the duodenum are overlooked, and unless the duodenal bulb has been grossly dilated because of long continued expansive pressure, the symptoms are attributed to a "spastic colon", although there is no roentgenographic or fluoroscopic evidence of spastic colon.

The intricacies of accurate diagnosis in gastrointestinal disorder warrant the repeated admonition of attention to the slightest detail. In these cases, that detailed attention should be focussed on the second and third portions of the duodenum.

In reviewing the available literature regarding pathologic changes in this region, one frequently encounters the term "characteristic roentgenologic picture". Roentgenograms cannot possibly demonstrate the condition, except when a fair degree of duodenal dilatation has taken place. All evidence confirming diagnosis must, of necessity, be fluoroscopic and is obtainable only by manipulation of the fluoroscopic table, and studying the patient, in reality, the barium column with the patient in various positions. This is important because some one particular position will serve best to corroborate diagnosis.

During fluoroscopic examination of these patients, most evident is the presence of antiperistalsis or reverse peristalsis in the second and third portions of the duodenum, the column of barium reaching the point of compression at about the terminus of the latter, then being unable to follow through, antiperistaltic waves of muscular action carry it back to the pylorus with resistance present at this point, with the result that there is produced an endless churning back and forth of the barium column between these two points. The food column acts in exactly similar manner.

Owing to the increased intensity of the peristaltic wave because of meeting such obstruction, and in attempting to overcome it, after some time, a secondary dilatation of the duodenum takes place in order to accommodate the increased food content, so that in a large percentage of cases, a duodenum of more than usual width and caliber is found.

Because of the inability of the duodenum to rid itself in a normal manner of this churning mass, an irritating mechanical friction of the duodenal mucosa takes place, even though the diet may be free from roughage and irritant fibre material, and a duodenitis is produced, manifesting itself roentgenologically by a fairly constant feathery irregularity of the duodenal outline.

Such changes are not as marked in the region of the bulb itself, because at this point the reverse pressure exerted against the pylorus is not as great as that at the point of yielding. Some relief of the intraduodenal pressure is obtained by food regurgitating through the pylorus into the stomach, at the same time releasing some of the pressure exerted against the compression point, but in no way influencing the vicious circle which has become established.

All of the duodenal wall changes are dependent entirely on the degree of compression; in only extreme cases are complete fixation and obstruction established. More often than not the food column, or, as one sees it fluoroscopically, the barium column, is propelled by peristalsis against the compressed barrier, and a small or large amount, varying in the individual case, is able to trickle through. The remainder is carried by the peristaltic action set up, backward toward the pylorus, then once again toward the jejunum, and a bit more gets through. This procedure repeats itself endlessly. The amount of compression exerted on the duodenum by the compressing artery naturally determines the amount of food or barium which is able to pass by and onward down the intestinal tract.

In those cases in which the syndrome has been present over a long period, absolute stasis in the doudenum is sometimes noted, brought about through a fatigue inertia of the smooth muscle from overwork, propelling itself against an unyielding force. In these cases the associated degree of duodenal dilatation is often extensive. Oblique observation, the patient lying in the left lateral or left oblique position, with the hips elevated, in most cases will demonstrate fluoroscopically a partial or even total release of the compression, and the barium column will pass onward and downward in the intestinal tract propelled by peristaltic action. This observation is of particular diagnostic significance and therefore to be stressed. Placing the patient in the partial Trendelenburg position and comparing the changes taking place with those found when the patient is in the standing position will often reveal that the condition is aggravated or intensified in the latter position. The patient may be placed in a modified knee chest position face downward, and pillows placed under the lower abdomen and thighs, in which case a partial or total alleviation of the compression takes place.

Treatment

Medical management is usually adequate. In very few cases is surgery indicated.

When surgical therapy is indicated, the ideal approach appears to be duodenojejunostomy.

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Discussion

Dr. Felix Cunha, (San Francisco, Calif.):—Sometime ago in the gastroenterological clinic one of our internists found a case of beautiful reverse peristalsis starting about an inch to the right and about an inch below the umbilicus and going up toward the pylorus.

Being possessed of a quizzical mind he wanted to know what gives here. Well, I said, let's study it. So we studied it fluoroscopically under all kinds of conditions to see what was taking place.

That is when our attention was first called to this syndrome. Of course, when we looked into the literature, the past literature, of this syndrome, we found it scanty indeed.

Recently both Dr. Day and myself have been asked in San Francisco to take part in certain symposia regarding duodenal stasis and we have been agreeably surprised because so many men would come up afterwards and say, "I've had a case like that. I know that thing existed, but couldn't find out about it". We find a good many men don't know that this syndrome exists, and you have here a real answer to a good many of your duodenal problem cases.

If you are a surgeon and you open the abdomen, the picture is absolutely typical. See it once and you will never forget it.

A few weeks ago Dr. Day and I were operating on a patient with a tremendous sized left ovarian cyst pressing on the sigmoid and rectum and causing an obstinate constipation.

We opened the abdomen. There it was, you couldn't miss it. This duodenal syndrome in addition to the cyst. About four or six months ago, I had an artist present at one of these cases and he drew the anatomical landmarks for me.

Dr. Day and I went immediately from the hospital back to the office and I produced it. It was absolutely typical to the nth degree of what we just had seen.

The thing is to remember that there is such a thing as compression of the third portion of the duodenum by either a superior mesenteric vessel itself or by an aberrant branch.

Surgically you can remove the aberrant branch. I have read in the literature of men resecting the superior mesenteric artery itself where no ill results followed.

I don't know how that can be done and I wouldn't want to try it.

THE VALUE OF IMMEDIATE ROENTGEN EXAMINATION IN SEVERE UPPER GASTROINTESTINAL HEMORRHAGE*

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and

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We have reviewed the case histories of 87 patients who were admitted to one of several hospitals in or near Phoenix because of severe gastrointestinal hemorrhage. The patients were otherwise unselected. The series is small compared with many others reported recently and it is not our intention to present a statistical study but rather to discuss certain principles pertinent to our subject.

The patient who bleeds gravely is in actual or potential shock. Ordinarily this condition is treated by complete rest, even to the extent of excluding any examination necessitating movement of the patient. There are, however, statistics to support the thesis that an immdiate x-ray examination of the upper gastrointestinal tract performed as recommended by Hampton or as modified by Schatzki[5] does not apparently increase the hemorrhage. Our findings are consistent with this conclusion in that in none of our cases was there evidence of increased bleeding or the initiation of a new hemorrhage. On the other hand, in common with other authors, we cannot say that the bleeding was not prolonged. Warthin[6], for example, refers to a possible 3 per cent recurrent bleeding following the x-ray examination and Zamcheck[7] to 10 per cent of patients who bled severely some time after the examination. Crohn and Janowitz[3] state that "we have seen enough hemorrhages initiated during radiologic examinations to make us wary of this method".

It would seem prudent, therefore, on the basis of the potential hazard to consider critically a recent recommendation[6] that "emergency gastrointestinal x-ray examination of all patients over forty years of age . . . should be done . . . as soon as they have been brought out of shock and regardless of previously diagnosed gastrointestinal lesions". The justification for this attitude would be that the immediate management of the actively bleeding patient might be changed by an emergency x-ray or that data important to the conduct of the case is demonstrable during active bleeding that will not be found ten days after bleeding ceases. It has been our purpose to determine whether indeed this justification exists. We shall not be concerned at this time with whether or when such a patient should be operated upon.

The x-ray examination is performed to find the cause and site of bleeding. It will be of interest first to determine the efficiency of the procedure. In our

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series we had a number of undiagnosed cases and our diagnostic efficiency was not high. In our 87 cases, the cause of hemorrhage was established by the initial x-ray in only 39, or slightly less than half. Subsequent events such as surgery, gastroscopy or autopsy established the diagnosis in 14 additional cases. In the 34 remaining cases, over one-third of the total, we do not yet know why the patient bled. If we had accepted an "ulcer history" as indicating the diagnosis, only 16 cases would remain undiagnosed but we shall discuss later why we did not accept this criterion alone. Our figures are modified by the following: (1) Several radiologists made the examinations but all were qualified. (2) The material was obtained from several hospitals but one or both of the present authors personally saw the majority of the patients at least in consultation. (3) A follow-up was available in a high percentage. (4) Only in 29 instances was the x-ray examination made within four days of admission but several others were examined while still actively bleeding but at a later period.

Our results are not significantly different from others in the literature. Thus, in more than 1,000 cases analyzed by Jones[4] about one-third were acute lesions not diagnosed by x-ray. They include acute gastritis, ulcer by gastroscopy, bleeding in the stomach at gastroscopy but no lesion found at postmortem. Two-thirds were "other radiologically negative cases". Jones apparently did not limit his group to severe bleeding but the figures are not much different when this is done. Warthin[6], for example, found that no diagnosis could be established in 16 per cent and was incorrect in 14 per cent. In another 4 per cent, the procedure was not completed. Apparently, in at least one-third of patients with severe gastrointestinal bleeding, the cause will not be found correctly at the initial x-ray examination. In fact, our batting average was not greatly improved by repeated examinations.

In order to examine the reason for this poor showing, we analyzed the causes of hemorrhage that were discovered. In the 39 cases in which the initial x-ray examination established a diagnosis, 26 were due to peptic ulcer, esophageal varices in 11, diaphragmatic hernia in 1, and carcinoma of the stomach in 1. In 15 additional cases in which a diagnosis was established subsequently, 1 was a gastric ulcer, 2 duodenal ulcer, hypertrophic gastritis 3, varices 4, leiomyosarcoma in a diverticulum of the jejunum 1, necrotizing arteritis 1, intestinal infarction 1, Meckel's diverticulum 1. In one case, autopsy failed to disclose the source of the hemorrhage. Hence, 29 out of 54 cases were due to peptic ulcer, 3 to hypertrophic gastritis, 15 to esophageal varices. In view of our diagnostic criteria, these figures are not inconsistent with the literature. Thus, Bockus[2] estimates that 60-75 per cent of all massive hemorrhage into the upper gastrointestinal tract is due to peptic ulcer. Jones found proven or probable peptic ulcer in over 90 per cent of his cases. If we group together peptic ulcer, gastritis and esophageal varices, there is general agreement that we will include well over 90 per cent of the cases (95 per cent, Jones; 93 per cent, Warthin; 90 per cent in our group). Furthermore, if we consider the remaining causes,

we would rarely expect a diagnostic x-ray during bleeding that would not be revealed even more efficiently after bleeding has stopped when the examination could be made more thoroughly. There is little doubt, therefore, that the major need in the immediate management of potential surgical cases is to exclude esophageal varices, which will affect the decision to operate.

It is important to point out here that the x-ray examination for varices is made best with a "dry" esophagus, i.e., when the esophagus has not been moistened by a previous "thin barium mixture", with the esophagus examined incidentally during the gastrointestinal study. The examination is most rewarding when the radiologist is aware of the problem and when the examination is limited, at least at the one sitting, exclusively to the question of varices. No manipulation is required. Indeed, most cases could be examined without fluoroscopy and at the bedside. The x-ray examination is necessary, particularly when a clinical diagnosis of hepatic cirrhosis cannot be established clinically. It has been stated[4] that in the majority of instances of varices due to cirrhosis that bleed, splenomegaly would be found and/or spider nevi, but this has not been our experience.

In our opinion, the diagnosis of peptic ulcer as the cause of the bleeding cannot be sustained on the basis of the clinical history alone. The "ulcer history" can be misleading both pro and con. In our 26 ulcer cases diagnosed by the initial x-ray, a positive ulcer history was obtained in 21 and was absent in 5. In the additional 14 cases diagnosed subsequently, the 6 who were found to have ulcer or gastritis, had a history of ulcer. The remainder did not. Eighteen patients in whom a diagnosis has still not been established, had "positive ulcer histories". The experience of Alsobrook[1] is comparable. In his 87 patients, 48 were diagnosed as duodenal ulcer prior to the hemorrhage and 30 gave symptoms of peptic ulcer for various periods of time. These figures suggest that while 15-25 per cent of patients with severe hemorrhage due to peptic ulcer do not give an "ulcer history", most do. On the other hand, there are a not insignificant group who give an acceptable "ulcer history" where an ulcer is not found even after a long follow-up. There were 18 of these in our series. How many had an ulcer that healed before the x-ray examination was made, or who suffered from gastritis which could not be demonstrated at immediate or later examination, we are unable to say. Schindler quotes the experience of Piedro de la Vasca that 10 per cent of gross hemorrhage is due to gastritis and Schindler himself is quoted[2] as considering this a conservative figure. At least 5 per cent of our cases bled severely as the result of gastritis.

We have stated that there should be a prompt search specifically for varices when the treatment may not be simply expectant. When the decision is to operate, should an urgent x-ray examination of the stomach, duodenum and small bowel be made? It is our opinion that this is to be determined largely on the individual basis. The delay and hazard of x-ray must be weighed against the information, sometimes inaccurate, that might be obtained.

When, on the other hand, the treatment is to be expectant, the x-ray examination can be justified only if data, important to the patient rather than to the physician, might otherwise be lost. Bockus states that in about 25 per cent of cases of massive hemorrhage studied within 2-3 weeks after the cessation of bleeding, we shall fail to establish unequivocally the cause and site of hemorrhage. Our data suggests an even higher percentage. This is not surprising since some ulcers heal in a few days, gastritis may subside and not infrequently, as in one of our cases, postmortem fails to demonstrate why the patient bled to death. There is little doubt that in some of these instances (2 in our group) an urgent x-ray will show an ulcer which will not be demonstrable 10 days later, but it must also be remembered that the roentgen interpretation is not infallible. We recall that in Warthin's series, an incorrect diagnosis was made in 14 per cent and in our small series, an occasional error was found when autopsy was available. If there are added the cases in which no diagnosis could be made, it is apparent that the x-ray examination is not only of limited value but of limited accuracy. Furthermore, it matters little in the actual management of a patient to *know* that an ulcer was present 10 days ago which is now healed, as compared with suspecting it strongly. Therefore, it seems to us that the urgent x-ray examination is not essential as a routine procedure. We feel that a practical compromise is to x-ray those nonsurgical cases who have bled before and a diagnosis has not been previously established. An occasional case will occur in which the patient bleeds from a new lesion, the previously demonstrated disease remaining quiescent. Yet from the point of view of practical management, this would be limited to the instance of a patient with hepatic cirrhosis who develops an exsanguinating peptic ulcer.

This discussion has been limited to the radiologic examination of the patient while he is actively bleeding. It should be hardly necessary to recall that bleeding may originate anywhere in the gastrointestinal tract and from a variety of causes other than those we have been discussing at length. When the patient is examined after the bleeding has stopped, he must be studied thoroughly with respect to all of the various lesions that have been known to bleed. Such conditions as ulcerating myoma in the esophagus, stomach or small bowel, carcinoma, hiatus hernia and diverticulum are some that may be demonstrable radiologically when the examination is meticulous. Massive bleeding, however, may occasionally occur as the result of a disease that is not primarily gastrointestinal.

Summary

Eighty-seven cases of severe gastrointestinal bleeding have been reviewed with respect to the advisability of performing an urgent radiologic examination as a routine procedure. The conclusion is reached the examination should be done only as a calculated risk. With uncontrolled hemorrhage, varices should be excluded promptly. This can be done if necessary without moving the patient from his bed and without manipulation. When a patient is to be operated, an x-ray examination of the stomach, duodenum and small bowel may be desirable

in the individual case if the procedure is expected to disclose information of value in immediate management. There is no urgent reason for subjecting other patients to x-ray unless the hemorrhage is recurring and is previously undiagnosed.

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DISCUSSION

Dr. Maurice Feldman (Baltimore, Md.):—For the purpose of a roentgenologic study we prefer to place ulcer cases into two categories, one for diagnosis, the other for check-up. Those cases that are urgent for diagnosis we believe that an x-ray should be made. The other group, those for check-up to find whether healing has taken place, we prefer to wait until a reasonable length of time has elapsed.

It has long been known that a careful x-ray examination of the stomach is not too great a hazard in cases of gastric hemorrhage. There has, however, been some reluctancy to carry out this form of examination during or immediately following massive bleeding of the stomach. I agree with the authors that an urgent x-ray examination is not always essential as a routine procedure.

There are many pathologic conditions besides peptic ulcer which produce gastric bleeding. The authors have shown that a large proportion of their cases were incorrectly diagnosed at the initial x-ray examination. Besides there were a number of cases in which no cause could be found. I wonder how many of these cases were due to prolapse of the gastric mucosa, since this condition commonly produces various degrees of hemorrhage.

Although in recent years, roentgen examination of the stomach during, or immediately following gastric hemorrhage has been recommended, it is our belief that it should be postponed whenever possible during active massive hematemesis or when a patient is in severe shock. In the latter case a small amount of barium solution can be used without too great a risk, if one avoids undue compression. It is important to caution not to overload the stomach with barium. It has been our experience that ordinarily most patients with bleeding are not harmed nor have any ill effects following the x-ray investigation.

It is important to stress that all cases of hemorrhage are not due to peptic ulcer and for this reason it is necessary to utilize this procedure when possible

to determine the cause, since the proper treatment of the patient may be jeopardized if the x-ray examination is not performed.

I should also like to emphasize that occasionally a gastric hemorrhage may be associated with perforation and this should be borne in mind when x-ray examination of the stomach is contemplated. It has been found that over 5 per cent of peptic ulcer cases in which hemorrhage was the chief cause of death were associated with perforation. For this reason it might be well for the roentgenologist to take a preliminary film of the abdomen to note for a possible perforation before barium is administered.

I am glad to note that the authors were most conservative and recommended that x-ray studies should be made on a selective basis rather than indiscriminately.

Dr. Michael W. Shutkin (Milwaukee, Wisc.):—I think a great responsibility rests principally with the gastroenterologist who at least in the early stages of the massive hemorrhage is often at the bedside. I agree with the authors performing an early roentgenologic study on the patient without a history of peptic ulcer or alcoholism. It is very disheartening to decide what to do with the patient in shock, bleeding profusely and the surgeon reluctant to operate in the face of such a serious condition. If we can contribute an accurate, early diagnosis to the surgeon we shall, in a great number of cases, save lives. You cannot expect the surgeon to operate on the patient with massive hemorrhage and in deep shock.

We oppose surgery for the patient with massive upper gastrointestinal hemorrhage of unknown etiology. We prefer to treat those patients medically. We also prefer to perform a roentgenologic study even in the face of massive hemorrhage without shock and hope at least to perform a logical act of mercy. I would like to emphasize that varices not only occur in the terminal esophagus but occur in the stomach as well and too often the roentgenologist fails to consider the possibility of large varices in the stomach in the presence of massive hemorrhage. Furthermore, in the face of demonstrable ulceration, surgical exploration of that stomach absolutely is required. It is mandatory that the hiatus portion of the stomach, namely the cardia, be explored at the same time.

Dr. Marcy L. Sussman (Phoenix, Ariz.):—I would like to tell Dr. Feldman that the patients we referred to were examined several times and evidence of prolapse of the gastric mucosa was not obtained.

I think I have to defend the subject of gastritis because I think there is a more or less specific x-ray finding which is associated with a gastrointestinal disturbance much like an ulcer syndrome, but with some differences. Some of these patients bleed and no longer bleed after resection. I agree with Dr. Feldman that there are patients who show a constant gastric deformity and who, on occasion, have bled more or less. On thorough exploration, on many occasions no ulcer is found. I do not insist on the designation "gastritis" for these cases but I do not know a better one.

THE DETECTION OF COLONIC LESIONS BY DOUBLE CONTRAST AND HIGH VOLTAGE RADIOGRAPHY*

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For nearly twenty-eight years after Roentgen discovered the x-ray, radiologists contented themselves with making a *single* film of the full colon, depending largely on their fluroscopic findings for a diagnosis. The first improvements made in the examination of the colon were by Fisher of Germany in 1925 and Weber of the Mayo Clinic a year or so later. They are credited with adding to the single film the postevacuation projection and the postevacuation air contrast study. Their method has been considered the regular or conventional procedure which is universally used today.

A further improvement was made by Stevenson and Moreton of Temple, Texas, in 1948. This new procedure consisted of filling the left side of the colon with the least possible amount of barium suspension, then immediately adding air in such a way as to force the barium around to the cecum. By this method the examiner is able to control the amount of barium introduced before the air is added, whereas by the old method, the amount of barium remaining in the colon after evacuation depended solely on the patient.

Mr. R. K. was first studied by the old postevacuation air contrast technic which showed a questionable polypoid lesion in the sigmoid. This is a good example of the patient expelling an excessive amount of barium before the air was added, resulting in a poor contrast. At a later date, we made two studies on this patient, using the new technic and no pathology was found.

It is hoped that this discussion will not give the wrong impression relative to the value of the postevacuation air contrast study. If at any time a suspected lesion is seen in the conventional examination, much can be gained by adding air and this has been well known for years. When an air contrast study is indicated, however, the new technic gives a better result and a better over-all coating of the colon wall.

This is well demonstrated in the films of two patients on whom we made studies by the old and the new technics.

The chief objection to the use of the Stevenson-Moreton method was the rapid drying of the barium suspension which they recommended.

Unless the films were made in rapid succession, frequently after the third film, all others would show dehydration.

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*Read before the Eighteenth Annual Convention of the National Gastroenterological Association, Los Angeles, Calif., 12, 13, 14 October 1953.

A new preparation of colloidal barium in suspension, sold under the name of Baridol, dehydrates less rapidly, permitting more time for the taking of films and also forming a more uniform coating of the mucosa of the colon. Baridol is a thick mixture and will not easily flow by gravity, and if it is to be used satisfactorily, a booster pump is required.

For a time, Dr. Stevenson dispensed with the conventional study and was depending entirely upon the air contrast examination for a diagnosis and for about one year we followed this routine. Fearing that some of the larger lesions were being missed, especially those in the right colon, it was thought wise to do the air contrast study on one day and the conventional study a day or so later. This is considered the most desirable examination.

Such a routine meant a second visit and a second preparation for the patient. Even I would object to taking castor oil twice in one week. Also, there is a third objection. Patients very frequently were unable to expel enough of the air to be comfortable before leaving the department, making it necessary to give a relief enema for the patient's comfort.

Soon it was considered logical to add barium to the relief enema. The small amount of air remaining did not interfere with complete filling of the colon; and if tannic acid were added to the barium suspension, a good relief pattern was obtained in the evacuation film. Very often the additional information obtained either from the air study or the conventional examination was enough to make a conclusive diagnosis.

A double study was made on Mrs. B. D. who gave a history of bleeding for one month with a negative sigmoidoscopic examination. A film of the sigmoid showed a questionable filling defect. The air contrast films also showed a questionable lesion appearing as a ring-like density with abnormal variation in the outline of the wall. In the conventional study immediately following the air contrast, the film of the full colon failed to show the filling defect. The lesion is demonstrable, however, in the evacuation film. I am showing this case as a good example of the value of the double study.

The colon study of Mrs. R. S. is another good example of the value of the double study, since the conventional study made prior to the double study was not conclusive. In the initial conventional study a film of the sigmoid showed a questionable narrowing which was not detected in the full colon. In the evacuation film the sigmoid was obscured by the filled ileum. Because of the history of bleeding, and the information obtained in the first film, a double study was carried out. In this study the air contrast films showed narrowing and a filling defect in the sigmoid. The evacuation film added additional information. From the findings noted in the double study, a diagnosis of constricting polypoid lesion was made and this was confirmed at surgery.

In the roentgenograms of the four following patients, the polypi seen in the air contrast were also visible in the evacuation films. With the additional in-

formation obtained from the evacuation films a diagnosis of polypi was made and these were found at surgery.

In our office for the past sixteen months a double study has been made on one day in all cases in which an air contrast was considered necessary. The indications for the double study were:

1. A polyp or carcinoma seen endoscopically
2. A history of a polyp or carcinoma having been removed
3. Bleeding from the colon

Bleeding from the colon calls for the most thorough examination possible. All too frequently, a diagnosis of bleeding from hemorrhoids is made without further study.

Mr. G. G. first noticed bleeding with both dark and bright red blood in 1948. A hemorrhoidectomy was performed at that time but the bleeding continued. Subsequent conventional barium enema studies and proctosigmoidoscopic examination failed to demonstrate the polyp that was found in the air contrast study made in 1953. A polyp ½ x 1 cm. on a 1 cm. pedicle was removed.

Another indication for a double study is a lesion seen endoscopically and the following is such a case: Mrs. R. S. gave a history of dark bleeding for eight months, pain in the lower abdomen, and loss of weight. Endoscopic examination showed large internal hemorrhoids and two small adenomas at four and five inches. The air contrast study demonstrated an advanced constricting carcinoma of the transverse colon and a polypoid lesion of the ascending colon. There is no doubt that the large constricting lesion in the transverse colon would have been seen by the conventional study. It is questionable, however, whether the polypoid lesion would have been recognized without the air contrast study. I think it important that a thorough study of the colon be made even though one lesion has been detected, since multiple lesions occur not infrequently.

In 1951, Mrs. I. B. had an adenoma removed through the anoscope and although she continued to bleed she was pacified by the diagnosis of hemorrhoids. In 1953, the double study showed multiple polypi. Five polypi were removed from the transverse colon and two from the descending colon, all on pedicles.

An endoscopic examination of Mrs. I. P. made in 1951, showed a polyp at six inches. The air contrast study made at that time failed to demonstrate this polyp but did show one in the sigmoid. The one visualized endoscopically was removed through the anoscope.

In 1951, the referring doctors were not easily convinced that such small polypi could be demonstrated by an air contrast study. This patient continued to bleed and five months later on re-examination, the polyp previously seen in the sigmoid was again demonstrated and was subsequently removed.

A third indication for the double study is the history of a polyp or carcinoma having been removed.

Mrs. D. R. was first seen in May, 1952. Some time prior to this she had had a resection of the sigmoid for carcinoma. In May, 1952, an air contrast made without the conventional study was interpreted as negative. In March, 1953, a constricting lesion of the ascending colon was demonstrated by the double study. A review of the air contrast made in 1952 shows clearly the undiagnosed polyp. It is possible that the polyp was present but was not visualized prior to surgery on the sigmoid. We know that it was present in May, 1952.

There has been a general belief that patients having a carcinoma of the colon should be re-examined yearly. If the early malignant lesion of this patient was not present prior to her surgery on the sigmoid, it had developed within a year. This raises the question, "How often should the patient known to have had carcinoma be re-examined?"

The third and most recent improvement in the method of examination of the colon is high voltage radiography, described by Gianturco and Miller of Urbana, Illinois, and Potter of Chicago. Gianturco and Miller are using a regular barium suspension with exposures varying from 120 to 130 kilovolts while Potter uses a thin barium mixture and exposures varying from 90 to 95 kilovolts.

These authors contend that high voltage radiography will show small filling defects not demonstrated by the old method of the thick barium and low voltage. Also, by this method, they feel that they are able to demonstrate equally well large filling defects and constricting and inflammatory lesions. This is likely a definite improvement over the old method and, in my opinion, should be the method of choice in the following: 1. for routine studies where no pathology is suspected; 2. ulcerative colitis; 3. a large palpable mass thought to be outside the colon and 4. obstructive lesions of the colon.

Through the courtesy of Dr. Gianturco, I would like to show a slide demonstrating that the higher the voltage used the greater is the penetration. On this slide there are three x-rays of a test tube of barium containing a marble made at 80, 100, and 120 kilovolts, respectively.

He has also been kind enough to lend me slides of the films of two patients with polypi and color photographs of the pathological findings.

This was a routine study using a thin barium mixture of 6 to 1 ratio, and a kilovoltage of 90. In the descending colon there was noted an oval filling defect, but in the air contrast study made at a later date, no lesion was demonstrated. From this, it is probably a safe conclusion that the filling defect was caused by fecal debris.

This is a similar study in which a filling defect was seen in the first conventional examination and not demonstrated in the follow-up air study made

at a later date. Differentiation between a defect produced by a lesion and one caused by feces is nearly impossible without a second study. Especially is this true in conventional examinations. Gianturco, realizing this, partially prepares his patient in his office by high enema. It must be emphasized that a clean colon is a paramount necessity for any method of examination.

In conventional studies feces displace barium appearing as an area of translucency and polypi or a polypoid lesion have the same appearance. Fecal debris seen in an air contrast study has a stringy or "swiss cheese" pattern while polypi or polypoid lesions appear as a round or oval mass. In polypi attached by a pedicle, the pedicle is smaller than the polyp itself and such a pattern is not observed in fecal debris.

The ability to differentiate between a polyp and feces in the air contrast study makes the air contrast a better examination for the detection of a small lesion.

Summary

The new air contrast technic and radiographic studies of the colon with high voltage technic are improved methods for detecting the small curable lesions. The author is proposing an additional method of improvement: namely, a double study carried out in one day. This double study consists of first making the air contrast examination followed in ten to fifteen minutes by complete filling of the colon with a 4 to 1 barium mixture.

Discussion

Dr. Benjamin R. Van Zwalenburg, (Grand Rapids, Mich.):—In my opinion this is a paper of very great practical value. I have no personal experience with Dr. Crozier's system of examination, but it is obviously careful work and his very moderate statements are commended.

We are becoming more critical and more demanding of our colon diagnosis.

There is real need for improvement. If it would help with those occasional bleeders we think it would be well worthwhile.

Essentially the new element here is in the order of procedure. After all we have most of us admitted that our conventional postevacuation double contrast film are not consistently good. Some are excellent and some are very poor. The patient either retains too much or too little in the terminal ileum. Once the barium has dried out it makes a poor air contrast film.

We have admired the excellent work of the single stage double contrast enemas developed by Moreton and by John Kaplan and Windholz here in California. We like the double contrast film of Dr. Crozier but we know and we want also the advantages of the conventional type of good fluoroscopy. The spot films and pre- and postevacuation films of Dr. Crozier are good.

In attempting to schedule the conventional type of an examination and then on another day the single stage double contrast enema and then perhaps on still another one or two days the all important recheck or confirmation, most doctors have been stopped by the excessive demands of time and nuisance value to the patient.

There has to be a limit to the castor oil.

Dr. Crozier has shown us how to get the advantages of both types of examination in a single day by reversing the order and in the doing first of the single stage double contrast enema and then on the same day a reasonably satisfactory examination of the conventional type.

This saving of time in and of castor oil brings the Moreton type of double contrast film within reach of those who also want the conventional barium filling and that to my mind is the most important feature of this paper.

In conclusion I commend Dr. Crozier's indication of the combined method for cases of bleeding.

So many systems of positioning have been described that I would like to emphasize that no one system of positioning for films is best for all cases.

No film shot blindly will compare with those individually positioned under fluoroscopy.

The examiner should use the fluoroscope to determine the best positions for each patient and himself fix each patient in those positions which will best include the particular loops that are in question.

It may be any degree of oblique position, but will rarely be AP or PA.

My opinion of this paper in a nutshell is that we are going to alter our routine to give Dr. Crozier's method a thorough trial in our hospital.

THE PATIENT WITH DIARRHEA*

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INTRODUCTION

The patient with chronic or recurrent diarrhea presents a problem which at times may tax the ingenuity of the most able physician.

Ryle's[6] observation is worth repeating: "For those of us who are chiefly concerned with clinical problems, it is often profitable to discuss the natural history of a single symptom; to consider its several origins and types; and generally to pass in review the diagnostic difficulties to which it may give rise. Such a survey should include a valuation of the methods available for the investigation of the symptom, and should have as one of its aims the practical consideration of how to rationalize treatment."

For some obscure reason this type of patient has not engaged the attention of many investigators. Fradkin's[4] admirable book is a very important contribution but it is probably of more help to the public health physician or to the specialist in gastrointestinal disease than to the general practitioner. The average textbook of medicine is singularly lacking or at most very brief in considering chronic diarrhea.

A study which reflects the observation of a physician in private practice in handling private patients would undoubtedly aid in determining how common chronic diarrhea actually is, what the most frequent types are, how diagnosis can be made and suggest methods of successful treatment. Up to the present there is only one such investigation available and that by Kantor[5]. The present study is a similar type of analysis for the purpose of comparison.

Bockus[2] and others[6] have observed that under ordinary circumstances and in a temperate climate diarrhea is not a common symptom. The gastroenterologist, however, encounters it quite often.

The acute diarrheas are omitted in this discussion because they are usually self-limited and of brief duration. It must be noted, however, that the acute diarrheas may activate latent gastrointestinal disease. A peptic ulcer which has caused little disturbance or an ulcerative colitis which has been quiescent may become reactivated during an attack of acute diarrhea.

The occurrence of an acute appendicitis during an attack of acute diarrhea, or so called "intestinal flu", is dangerous because the symptoms of appendicitis

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may be masked by the diarrhea and abdominal distress. It is important to realize that any acute diarrhea which does not subside within 24 to 48 hours may have serious underlying complications.

We are not concerned with infantile diarrheas which are of particular interest to the pediatrician.

A few of the studies on chronic diarrhea that are available are as follows:

One of the earliest studies based on autopsied and clinical material was that of Cabot and Emerson[3] which appeared in 1913. The next paper was the one quoted above, by Ryle[6] in 1924. Kantor's[5] paper appeared in 1935. Bockus'[2] excellent chapter in his text appeared in 1944. Fradkin's[4] book on diarrhea appeared in 1947. Sullivan's[7] paper on "Emotion and Diarrhea" was published in 1936, Baird's[1] paper in 1946. It must be apparent from these few citations that the subject of chronic diarrhea has not been exhausted from the standpoint of clinical investigation.

TABLE I

BASIS FOR THE CLINICAL CLASSIFICATION OF CHRONIC DIARRHEA

	Functional	Organic
1. Demonstrable lesion of the intestinal mucosa	0	+
2. Stools contain pus, blood, infectious bacteria or parasites.	0	+
3. Mucosal lesions may be seen through sigmoidoscope.	0	+
4. Anemia, fever, emaciation, dehydration or collapse.	0	+

CLASSIFICATION

Before we can discuss the various types of chronic diarrhea and their differential diagnosis, a classification is very desirable. Ryle[6] suggested an anatomical classification based on the site of origin of the symptom. Thus he considered chronic diarrhea caused by disease of the stomach, small intestine, large bowel and rectum and accessory glands like the pancreas. Bockus[2] modified this classification.

Fradkin[4] stated that a classification based on etiology was the only logical approach to this problem. Theoretically such a classification is an ideal one, practically I must agree with Kantor[5] who stated:

"In the present state of our knowledge, it is impossible to offer an etiological classification of the diarrheas. All that can be attempted is a crude division into functional and organic groups. The organic cases are characterized by the presence, the functional by the absence, of a demonstrable lesion of the intestinal mucosa. In organic diarrheas the stool contains pus, blood, infectious bacteria or parasites; the mucosal lesions may be seen through the proctoscope; there may be anemia, fever, emaciation, dehydration or collapse. In the functional diarrheas, these features are absent".

The basic features of this classification are shown in Table I.

For purposes of simplification and without greatly altering the value of Kantor's classification it has been modified as shown in Table II.

This classification has been of real help in evaluating the problem of chronic diarrhea.

The incidence of diarrhea in hospital practice is different than in private practice. Hospital statistics on chronic diarrhea are very meagre. Cabot and Emerson[3] reported such a study based on a clinical and postmortem observation of 640 patients.

As Kantor so ably stated "Statistics derived from the private practice of any one individual are notoriously personal and cannot be expected to apply too precisely to the experience of another physician. Yet there is a unity of viewpoint and a continuity of observation that may make their presentation of some interest to others".

TABLE II

CLINICAL CLASSIFICATION OF CHRONIC DIARRHEA
(Modified from Kantor)

Functional	Organic
1. Nervous Diarrhea, Irritable Colon	1. Infectious
2. Gastrogenous Diarrhea	A. Specific
3. Systemic	1. Amebiasis
a. Pellagra	2. Tuberculosis
b. Nontropical sprue	B. Nonspecific
4. Endocrine	1. Ulcerative colitis
a. Hyperthyroidism	2. Regional enteritis
b. Addison's Disease	2. Toxic
c. Pancreatic Disease	A. Exogenous—Arsenic, Mercury
5. Allergic	B. Endogenous—Uremia, Sepsis
	3. Neoplastic
	A. Benign
	B. Malignant
	4. Miscellaneous
	A. Diverticulitis
	B. Endometriosis

Kantor in an unselected series of 3,880 private patients complaining of various digestive troubles during a period of 18 years observed 390 cases of diarrhea an incidence of 10 per cent. In a period of 19 years the author observed 8,600 patients with various digestive troubles and of this group there were 525 patients with a primary complaint of diarrhea an incidence of about 6 per cent.

In Kantor's series there were 324 functional cases, 81 patients with organic disease and 12 of undetermined etiology.

In the present series there were 337 functional cases, 178 patients with organic disease and 10 of undetermined etiology.

Kantor also analyzed his private cases to determine what types of diarrhea were encountered in private practice. Table III summarizes the outstanding types of diarrhea in Kantor's group of private patients.

TABLE III

TYPES OF DIARRHEA IN 390 PRIVATE PATIENTS (KANTOR)

Functional		Organic	
1. Colonic instability ("nervous diarrhea")	210	1. Idiopathic ulcerative colitis	41
2. Gastrogenous	70	2. Tuberculosis	12
3. Simple or environmental	22	3. Postdysentery	10
4. Idiopathic steatorrhea	5	4. Regional ileitis	5
5. Allergic	5	5. Carcinoma of rectum	4
6. Compensatory	4	6. Acute bacillary dysentery (?)	3
7. Malabsorption	2	7. Amebic dysentery	3
8. Endocrine	2	8. Rectal stricture	1
9. Putrefactive	2	9. Amyloid disease	1
10. Permentative	2	10. Trichomonas	1
	324		81

A similar analysis which revealed the following was made in this study. See Table IV.

Bockus[2] has made an analysis of a group of patients from both hospital and office practice which is shown in Table V.

TABLE IV

TYPES OF DIARRHEA IN 525 PRIVATE CASES

Functional		Organic	
Irritable colon	288	Ulcerative colitis	93
Gastrogenous	18	Carcinoma	30
Pernicious Anemia	1	Regional enteritis	18
Dumping Syndrome	1	Post dysentery	18
Achlorhydria	4	Diverticulitis	11
Gastrojejunocolic fistula	2	Undiagnosed	10
Exophthalmic goitre	5	Ileojejunitis	6
Pancreatic disease	4	Endometriosis	3
Nontropical sprue	4	Diabetic nocturnal diarrhea	2
Allergic	6	Dyschesia	2
		Parasites	2
		Amebiasis	2
		Tuberculosis enteritis	1
		Benign papilloma of descending colon	1

Most of the other surveys and studies are either concerned with acute diarrhea, infantile diarrhea, epidemics in hospitals or institutions, and are in no way comparable to experience in private practice.

The present classification is of great value because it allows for a division into the two important groups of chronic diarrheas encountered in practice.

The group with functional diseases in which the prognosis is generally good, the results of therapy good.

The group of organic diarrheas usually the result of serious organic disease.

Diagnosis

The diagnosis of chronic diarrhea is based on the following criteria:

1. History.
2. Physical examination.
3. Stool examination.
4. Digital examination.
5. Proctosigmoidoscopic examination.
6. Barium enema studies.
7. Special studies.

1. In the history, the age of the patient is of significance. Bockus[2] has emphasized that ulcerative colitis occurs in young people. Gastrogenous diarrhea, diverticulosis and colonic carcinoma occur in older people. A diarrhea that has been present for over three years is not likely to be due to carcinoma.

2. In the physical examination Bockus has pointed out that diarrhea with abdominal distention may be due to regional enteritis, intestinal tuberculosis or malignant disease. A diarrhea with a mass in the lower quadrant may result from carcinoma of the colon, regional enteritis or granuloma.

3. Stool analysis is useful to rule out bacillary dysentery or amebic colitis.

4. Digital examination is necessary in the diagnosis of malignant disease, stricture, impaction and ulcerative colitis.

5. Proctosigmoidoscopy is important in the diagnosis of malignancy, ulcerative colitis and polyps.

6. Barium enema studies are of importance in the diagnosis of carcinoma, ulcerative colitis, polyposis, diverticulosis, and irritable colon. Mouth meal roentgen studies are valuable in the diagnosis of regional enteritis, sprue, and to demonstrate hypermotility in the digestive tract.

7. Special examinations: Fractional gastric analysis, basal metabolism determination, glucose tolerance tests and salt and water retention tests are indicated in hyperthyroidism, sprue, Addison's disease and gastrogenous diarrhea.

Differential Diagnosis

From a clinical standpoint the most important decision is whether one is dealing with a functional or an organic type of diarrhea. The character of the evacuation is of great importance. The most significant finding is the presence or absence of blood. In general the presence of blood in the evacuations indicates an organic diarrhea until ruled out by appropriate studies (it is possible to have an irritable colon and a bleeding hemorrhoid).

It is important to remember that out of every five patients with chronic diarrhea three will most likely have a functional type of diarrhea.

In the functional group the most conspicuous member is the patient with an irritable colon—the emotional diarrhea. The other members the gastrogenous, the allergic, the nontropical sprue, the patients with systemic diseases like hyperthyroidism, Addison's disease and pellagra, make up a comparatively smaller percentage.

In the organic groups the outstanding members as noted above are the ulcerative colitis, regional enteritis and carcinoma of the rectum and colon. The

TABLE V

THE VARIOUS CAUSES OF CHRONIC DIARRHEA (BOCKUS)
(Arranged in the Order of Their Frequency)*

1. Diarrhea of nervous origin (emotional diarrhea, neurogenic mucous colitis and neurogenic gastrointestinal hypermotility).
2. Chronic ulcerative colitis.
3. Carcinoma of the colon.
4. Gastrogenous diarrhea including the diarrhea following gastrojejunostomy and gastrojejunocolic fistula.
5. Constitutional disorders including allergy, goiter, diabetes and nephritis.
6. Nonspecific regional enteritis and ileocolitis.
7. Nutritional deficiency states.
8. Diarrhea due to constipation and the use of laxatives.
9. Defects in intestinal absorption (steatorrhea and mesenteric glandular disease).
10. Amebic colitis.
11. Bacillary dysentery.
12. Diseases of the gallbladder and pancreas.
13. Tuberculous enterocolitis.

*The incidence is estimated from cases encountered in office practice and the Graduate Hospital clinic.

metal poisonings with arsenic and mercury, the uremic colitides are not common. There was one case of tuberculous enteritis.

TREATMENT

In the treatment of chronic diarrhea, the following are important:

1. Rest.
2. Diet.
3. Medication.

1. *Rest:*—During an acute exacerbation, bed-rest may be necessary and hospitalization may be required.

2. *Diet:*—In severe cases, a liquid diet is probably all that can be tolerated. Milk is usually not well tolerated. Meat, tea, warm fruit juices, rice and potatoes are satisfactory for the average patient. In general, a diet of smooth type is indicated.

3. *Medications:*—(a) Codeine is a very useful drug. As pointed out by Ryle[6], it is one of the few drugs that is capable of quieting the hyperirritable digestive tract. Codeine is given alone or in combination with phenobarbital, grains one-quarter to one-half of each, twice or three times daily. There is little fear of addiction to codeine.

(b) The introduction of the anticholinergic drugs with their depressing effect on motility suggested that they might prove useful in the management of chronic diarrhea.

Banthine, prantal, antrenyl, pro-banthine and others have been tried in turn in the treatment of these patients.

The most dramatic effects have been noted in the patient with hypermotile, hyperirritable digestive tract where the barium sulfate can traverse the entire digestive tract in an hour or an hour and a half. The use of banthine, antrenyl and pro-banthine has worked well to cut down motility and to control a chronic diarrhea in many of these patients.

In others where the diarrhea resulted purely from an irritable colon with little or no hyperperistalsis and activity in the stomach or small intestine there has been very little help in controlling the diarrhea.

In addition to the anticholinergic drugs the methylcellulose tablets or the bulk producing preparations like karajel, mucara and metamucil have been helpful in producing an evacuation that has formation.

Specific Treatment of Specific Types of Chronic Diarrhea

Functional Group:—1. Nervous or emotional diarrhea, the most frequent of all types of diarrhea, is an expression of an anxiety state. In one individual the diarrhea may develop only at ordinary times when the bowels move or under conditions of stress. In others the patient may lose entire confidence in himself to control the activity of his bowel so that it becomes impossible for him to go to any social function or it may actually interfere with business or professional activities. To face the risk of being out of reach of a lavatory on these occasions becomes intolerable.

Nervous diarrheas are treated most effectively as follows:

a. Careful explanation to the patient of his condition with emphasis on the absence of organic disease.

b. Smooth diet with antispasmodics, sedatives and bulk producing preparations are usually of value. Anticholinergic drugs are useful in patients with marked hyperperistalsis and hypermotility.

c. Codeine phosphate alone or in combination with phenobarbital is reserved for the refractory patient.

Individuals who become reconciled to a life of invalidism have been rehabilitated by the use of minimal dosages of codein phosphate once or twice daily.

2. Gastrogenous diarrhea has been the basis for a great deal of discussion and some controversy. Ryle[6] had this to say about this subject:

"The textbooks of general medicine accord little or no space to the consideration of this interesting group of diarrheas, nor does it appear to be widely recognized in practice. Nevertheless it is one of the most important. Numerically it accounts for more cases than any other single group excepting the nervous group. In the majority of cases of gastric diarrhea there is a great diminution or complete absence of the free hydrochloric acid of the gastric juice, and to the extent that complete relief of the diarrhea is nearly always afforded by the therapeutic administration of dilute hydrochloric acid it would seem that the deficiency is in itself an essential factor".

The lack of hydrochloric acid cannot be the sole factor because we would expect all patients with pernicious anemia to have a chronic diarrhea. We know that this is not the case. There are many patients with pernicious anemia who complain of severe constipation and the number of patients with diarrhea is not unusual.

The clinical features of a case of simple gastrogenous diarrhea are as follows: The evacuations are not frequent, three or four stools in the course of the day being the usual number, though occasionally there may be as numerous as six or eight. They are unaccompanied by pain or colicky sensations. The stools are loose and unformed rather than fluid. They contain neither mucus nor blood.

A fractional test-meal in the majority of cases shows complete absence of free acid throughout the meal, and a very low curve of total acidity. Usually there is rapid emptying, the stomach sometimes being empty within a half to three-quarters of an hour instead of in the more usual period of two hours. A radiographic examination with an opaque meal shows a similar rapid emptying and rapid passage throughout the intestinal tract.

Good results in these patients have been obtained from the judicious use of small doses of banthine, antrenyl and similar anticholinergic drugs where hydrochloric acid did not relieve the symptom.

3. *Constitutional diarrheas:*—The underlying disease, pellagra, hyperthyroidism or Addison's disease must be treated.

4. *Nontropical sprue:*—Cortisone has been found valuable in therapy in dosage of 25 to 50 mg. daily orally.

5. *Allergic diarrheas:*—The antihistaminic drugs have not been of value.

Organic Diarrheas

1. The *specific infectious types* of diarrhea were represented mainly by amebiasis. There were only a few proven cases. Somehow the overwhelming

numbers anticipated in our returned veterans were not seen privately. The experience in the veteran's hospitals has probably been different.

2. *Chronic ulcerative colitis:*—The treatment has to be thorough and comprehensive. A high protein diet, multiple small blood transfusions and ACTH and cortisone are of value. Surgery has to be done in the complicated cases.

3. *Regional enteritis:*—The treatment of choice is surgical; either a one stage or two stage resection or simply a short circuiting operation.

4. *Carcinoma of the colon and rectum:*—Surgery is the only curative treatment.

5. *Toxic* group of diarrheas was not encountered in this study.

6. A *benign* tumor of the descending colon was the only one seen with persistent diarrhea. Surgical removal of the tumor resulted in a complete subsidence of diarrhea.

7. *Diverticulitis* was not a frequent cause of diarrhea. Usually the control of the diverticulitis resulted in control of the diarrhea.

8. Two interesting cases of *endometriosis* were seen. In both instances the diarrhea was definitely related to the menstrual period at which time it usually occurred and bleeding usually accompanied the diarrhea. Removal of the primary pelvic lesion and removal of the lesion in the rectum in one patient and in the rectosigmoid in the second patient was curative. A third patient with endometriosis seen in consultation was treated elsewhere.

Summary

1. Chronic diarrhea is a symptom of importance in daily practice.

2. The diagnosis of chronic diarrhea is usually established by the history, physical and digital examinations aided by proctosigmoidoscopic and barium enema studies.

3. The general treatment of chronic diarrhea is based on (a) rest, (b) diet and (c) medication.

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Discussion

Dr. William Z. Fradkin (Brooklyn, N. Y.):—Time will not permit a discussion of all the valuable clinical data presented by Dr. Shaiken. I would therefore like to emphasize one phase of Dr. Shaiken's contribution namely the importance of determining or attempting to determine the etiologic agent early in the management of the patient with diarrhea.

Dr. Shaiken surprisingly states that an etiologic classification is ideal but not practical because it is impossible of attainment in the present state of our knowledge. He is too modest. We can recognize today the various bacterial diarrheas, protozoan diarrheas, viral, allergic, mechanical, glandular, psychogenic and many others. Let us use our present knowledge and the methods now available to further develop the ideal etiologic classification which will help us in diagnosis and treatment and let us avoid the pitfalls and shortcomings of the functional and organic divisions.

The patient with diarrhea feels discouraged, anxious and confused. He already dieted himself to malnutrition, treated himself with all sorts of mixtures from the corner drugstore, traveled from physician to physician, from hospital to hospital with no permanent relief. These patients with chronic diarrhea appeal to us to find a more successful approach to their problem. Dr. Shaiken's presentation at this national convention is a step in the right direction.

It would not be fair after having traveled 3,000 miles for me not to reveal to you my objectives and hopes in this field the study of which has interested me for over 25 years. It would be a dream come true were we physicians as a national body able to educate the public through print, radio and even television that a diarrhea of over 4-5 days' duration requires a simple procedure at no cost to the patient but which may prevent chronicity, serious complications and radical surgical resections. This simple procedure would consist of sending a specimen of freshly passed stool to the nearest Board of Health Station for cytology and culture. This specimen would reveal the name and address of the private physician to whom a detailed report would be mailed.

By popularizing this simple procedure in every part of the country, carriers of intestinal pathogens would be readily discovered and properly cared for. The incidence of nonspecific diarrheal diseases would be greatly diminished. It would obviate the present confusion and difficulty in trying to isolate pathogens after sulfa drugs, antibiotics, barium and bismuth have been given. This simple procedure done under proper supervision would permit early screening of intestinal malignancies. It would discourage self-medication, and bring the patient to his physician earlier. It would reduce the promiscuous use of a large variety of antidiarrheal mixtures and lessen the chronicity of the disorder. Such a scientific approach on the part of the profession would tend to strengthen the confidence of the patient in his private physician.

Dr. Samuel S. Berger (Cleveland, Ohio):—Diarrhea can cause not only pain in the patient's abdomen but a pain in the neck for the physician or gastroenterologist.

I was very much interested in Dr. Fradkin's remarks as to the proper approach in the diagnosis of the diarrheas. I think that he has outlined a logical and correct method of dealing with diarrhea promptly and before serious results occur.

I should like to cite the instance of a woman, aged 60 years, who gave a history of diarrhea and abdominal pains of about 8 weeks' duration. History otherwise was essentially negative except for severe allergy. She is sensitive to a number of foods, consequently she had been on a restricted diet for a long time. She had 8-10 bowel movements in the 24 hours.

She did not notice blood or mucus in the stools. General physical examination was negative except for a mild hypochromic anemia and an elevation of temperature. Sigmoidoscopic examination revealed a normal appearing bowel. Barium enema was negative. The terminal ileum appeared normal. X-ray study of esophagus, stomach and duodenum was negative. The small intestine revealed a slight coarsening of the mucosal pattern which was thought to be due to a deficiency state. Gastric analysis was normal. Stool examinations revealed (repeatedly) almost a pure culture of proteus, which was found to be sensitive to neomycin and streptomycin. No antibiotics were used up to this time.

We did not know the significance of the overgrowth of proteus in the bowel and no one that I contacted had any experience with it. Several courses of neomycin and streptomycin were given with some change in the number and character of the stools. The proteus was inhibited but promptly reappeared in almost pure culture when the neomycin was discontinued. Since proteus infection of the urinary tract has been reported to respond well to furandantin we thought it might be similarly efficacious in the intestinal tract. We tried it but it induced nausea and vomiting after 2 days' trial and had to be discontinued.

We started ACTH gel in 40 unit doses. The response was dramatic, fever, abdominal discomfort and diarrhea became much improved but 40 units induced nervousness and a hyperkynetic state so that the dosage was reduced to 20 units and later 10 units daily which seemed quite adequate.

A definite diagnosis was not yet established. Another x-ray study of the gastrointestinal tract was done with essentially negative findings except the slight changes in the mucosal pattern of the small bowel. We began to feel that we were dealing with an ileojejunitis. Ten days later another x-ray study revealed essentially the same finding. The fourth study of the small intestines revealed slight but positive x-ray changes of the terminal ileum, thus making the diagnosis of terminal ileitis probable.

ACTH was continued along with the usual measures: Neomycin, short courses; streptomycin, sulfasuxidin or thalidine, etc.

Then, one day, the patient began to pass blood in the stools, rapidly increasing in severity and promptly becoming massive, with shock. As soon as shock was controlled with continuous transfusions, etc., exploratory laparotomy was done. The terminal ileum was found to be thickened and contained clots. About 20 inches of the ileum and also the cecum was removed. The walls of the resected portion of the ileum was thickened and the mucosa showed the characteristic cobblestone appearance. There were numerous superficial ulcerations present. There was a sharp line of demarcation, about 18 inches above the cecum. The cecum was normal.

Here, then, is a case of diarrhea in a woman 60 years of age which proved to be so-called terminal ileitis—the diagnosis being suspected only after all other findings were repeatedly negative. Only after repeated examinations, clinical and x-ray, did the early changes in the terminal ileum become evident.

The role of the proteus, in practically pure culture, in the production of the symptomatology and its relationship if any to the pathology, I am unable to evaluate. Perhaps Dr. Fradkin, or someone here, might throw some light on it.

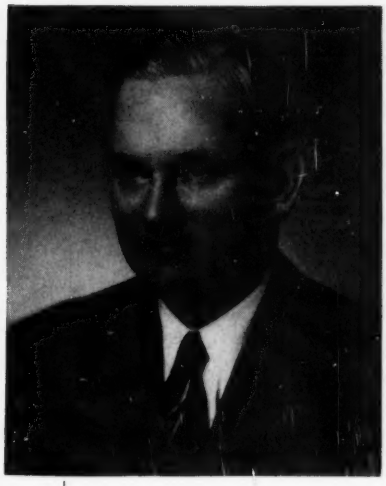
Terminal ileitis at the age of 60 is unusual. Hemorrhage, likewise, is not part of the picture. I wonder whether ACTH had any bearing on the production of the ulcerations and the hemorrhages? Has anyone had any experience along this line?

Dr. Joseph Shaiken (Milwaukee, Wisc.):—First I want to thank Dr. Fradkin for his discussion. I know he has done a wonderful job on the subject of diarrhea. He has written an excellent book.

I would like to suggest that each individual person use whatever helps him understand the problem. It happens that the classification that I have given you here is one that helps me evaluate the patients that come to me and I find it useful.

Dr. Fradkin's suggestion about having the stools examined is excellent and I am heartily in favor of it.

In reply to Dr. Berger I have not seen any proteus infections of the bowel producing diarrhea and I cannot help him.



President's Message

The Committee on Constitution and By-laws presented a proposed Constitution and By-laws for the American College of Gastroenterology to the Executive Committee of the National Gastroenterological Association which carefully considered and unanimously approved an amended version.

The next step will be to submit the Constitution and By-laws to the National Council, which will meet in Milwaukee, Wisc.

Our new organization will incorporate all the good features of the National Gastroenterological Association and provide some changes which will make the American College of Gastroenterology a more effective organization to advance the cause of gastroenterology.

The aims of the College will be to establish an organization composed of qualified physicians of high standing, engaged in the practice of gastroenterology and its allied fields, and to maintain and advance the highest standards in medical education, medical practice and research in the field of gastroenterology.

Many of our membership have been concerned about their status in the New American College of Gastroenterology. The new By-laws will provide that all Fellows, Life Fellows, Honorary Fellows, Associate Fellows and Members of the present organization are to be accepted in their present classifications in the American College of Gastroenterology.

Some have asked what are the advantages of the change?

First—the American College of Gastroenterology hopes to take more effective steps in advancing the specialty of gastroenterology. Second—it hopes to raise the standards of the specialty and Third—to make it possible for young graduates of Medicine to qualify as gastroenterologists.

Time forbids enumeration of further benefits, but as the College passes through its formative stages we will keep you informed as to progress on our new organization.

Sigurd W. Johnson

EDITORIAL

Gastrointestinal Symptoms Caused by Cardiac Medications

Several years ago, a prominent cardiologist called attention to five groups of remedies used in the treatment of heart disease which may cause gastrointestinal upsets. These drugs are digitalis, xanthines, ammonium and/or potassium chloride, quinidine and mercurial diuretics.

More recently attention was called to a form of generalized edema, especially in women, in whom laboratory tests failed to show abnormal states. The use of some of these preparations caused loss of appetite, nausea, vomiting and heartburn. Not getting results, digitalis was prescribed which increased the gastrointestinal irritation and added to the previous symptoms of dizziness, headache, tinnitus and vertigo.

Over-digitalization is the signal to discontinue the drug because of the possibility of causing severe digitalis poisoning. In many patients, adverse effects are manifested by digitalis before over-digitalization occurs and the symptoms should be recognized by the physician. Nausea, vomiting, green or yellow vision and small, watery bowel movements with or without rectal irritation, are some of the premonitory signs. The patient or members of the family should be forewarned, especially where large doses of the drug are given to attain rapid results.

Permanent injury due to over-dosage of digitalis may cause the liver to enlarge, the pulse to become slow (bradycardia) and frequent ventricular beats to appear.

The vomiting caused by the digitalis may be of central origin, especially when it is administered intravenously and the reaction of the stomach acts as a cardiac reflex over the sympathetic nervous system to the vomiting center. Prolonged vomiting produces congestion and inflammation of the gastric mucous membrane which is similar to that found in acute gastritis.

Many of the xanthine preparations not infrequently affect the gastrointestinal tract. Theobromine preparations in the presence of hyperacidity, may cause nausea and heartburn. By prescribing these preparations before meals and giving the patient an antacid or adsorbent after the meal, discomfort may be obviated. An interesting observation, when prescribing theobromine with sodium salicylate is that it may act as an intestinal irritant causing small and frequent watery stools, incontinence of feces and even thrombotic hemorrhoids. Adding four drops of tincture of opium to each dose will prevent the diarrhea.

Ammonium chloride also affects the gastrointestinal tract. Prescribing enteric coated tablets of ammonium chloride may help in preventing irritation, but if continued for a length of time, gastritis may occur.

Quinidine sulfate may also cause diarrhea in sensitive patients and adding a few drops of tincture of opium will prevent intestinal irritation. When this fails to overcome the intestinal irritation, quinine sulfate may be substituted for the quinidine.

Mercurial diuretics, when given intravenously or intramuscularly, have little if any deleterious effect upon the gastrointestinal tract. Patients who complain of abdominal cramps should have their stool examined for occult blood.

Rectal suppositories containing diuretic medications, especially mercury, at times have caused irritation, inflammation and even sloughing of the rectal mucosa.

SAMUEL WEISS, M D.

REGIONAL ACTIVITIES

PROGRAM

CENTRAL REGIONAL MEETING

NATIONAL GASTROENTEROLOGICAL ASSOCIATION

Sunday, 28 March 1954

East Room

SCHROEDER HOTEL

Milwaukee, Wisconsin

BUSINESS SESSION

9:00 A.M. Meeting of the Executive Committee of the National Gastroenterological Association.

9:30 A.M. Meeting of the National Council of the National Gastroenterological Association.

12:30 P.M. National Council luncheon.

1:30 P.M. Registration—5th Floor.

1:45 P.M. Introductions and announcements.

Dr. Joseph Shaiken, Central Regional Representative, National Gastroenterological Association, General Chairman.

a) Dr. Sigurd W. Johnsen, President, National Gastroenterological Association.

b) Dr. John S. Hirschboeck, Dean, Marquette University, School of Medicine.

c) Dr. William S. Middleton, Dean, University of Wisconsin, School of Medicine.

SCIENTIFIC SESSION

FIRST SESSION

DR. SIGURD W. JOHNSEN, President, National Gastroenterological Association, presiding.

2:00 P.M.

1. "The Genetic Factor of Familial Multiple Polyposis Coli".

Speaker

DR. ROBERT T. MCCARTY, Milwaukee, Wisc. Associate Professor of Surgery, Marquette University, School of Medicine.

General Discussion

2:30 P.M.

2. "Diverticulitis and Carcinoma of the Colon".

Speaker

DR. JAMES A. FERGUSON, Grand Rapids, Mich. Consulting Surgeon, Ferguson-Droste-Ferguson Rectal Clinic and Hospital.

Discussion to be opened by:

DR. CARL W. EBERBACH, Milwaukee, Wisc. Clinical Professor of Surgery, Marquette University, School of Medicine.

3:00 P.M.

3. "Conservative Management of Occlusive Diseases of the Esophagus".

Speaker

DR. KARVER L. PUESTOW, Madison, Wisc. Professor of Medicine, University of Wisconsin, School of Medicine.

Discussion to be opened by:

DR. GERHARD STRAUSS, Milwaukee, Wisc. Clinical Professor and Director of the Division of Otolaryngology, Marquette University, School of Medicine.

3:30 P.M. Intermission

SECOND SESSION

DR. LYNN A. FERGUSON, President-elect, National Gastroenterological Association, presiding.

3:40 P.M.

4. "Present Day Management of Benign Ulcerative Intestinal Disease".

Speaker

DR. J. ARNOLD BARGEN, Rochester, Minn. Professor of Medicine, University of Minesota, School of Medicine; Mayo Clinic. (By invitation).

General Discussion.

4:10 P.M.

5. "Diagnosis and Treatment of Pancreatic Disease".

Speaker

DR. PHILIP THOREK, Chicago, Ill. Associate Professor of Surgery, University of Illinois, School of Medicine. (By invitation).

General Discussion.

4:40 P.M.

6. "Neurovascular Mechanism of Gastric Ulcer Formation".

Speakers

DR. H. B. BENJAMIN, Milwaukee, Wisc. Assistant Professor of Anatomy, Marquette University, School of Medicine. (By invitation) and DR. MARVIN WAGNER, Milwaukee, Wisc. Associate in Anatomy, Marquette University, School of Medicine. (By invitation).

Discussion to be opened by:

DR. JAMES SMITH, Milwaukee, Wisc. Professor of Physiology, Marquette University, School of Medicine.

ABSTRACTS FOR GASTROENTEROLOGISTS

LIVER AND BILIARY TRACT

THE SILENT GALLSTONE: Chas. D. Branch. Surg. Gynec. & Obst., pp. 246-247, (Aug.), 1953.

If the problem of cholelithiasis is considered from the standpoint of probable complications, it is concluded that one must question the benign character of a stone. The gallstone is the main factor in the production of acute cholecystitis, common duct stones, and carcinoma of the gallbladder. In addition, cardiologists have been impressed with the frequent association of coronary heart disease and gallbladder disease. The silent stone like a silent volcano might erupt at any time. Therefore, cholecystectomy should be performed at the time of the discovery of the stone and not when complications arise.

J. R. VAN DYNE

HYPOKALEMIA IN LIVER CELL FAILURE: Edward L. Artman and Robert A. Wise. Am. J. Med. 15:459, (Oct.), 1953.

Twenty-five of 30 cases of acute liver failure showed hypopotassemia either on admission or during the course of treatment. Anorexia, nausea, vomiting and diarrhea causing decreased potassium intake and exaggerated protein catabolism and glycogenolysis producing increased renal loss of this ion were responsible for the initial hypokalemia. On the other hand, potassium free infusions, paracenteses and mercurial diuretics as well as glycogenesis and protein anabolism lowered the serum potassium during the period of treatment. Hypopotassemia may be an aggravating factor in the course of hepatic insufficiency, therefore, serum potassium levels and EKG tracings should be observed in this condition.

H. B. EISENSTADT

TRANSIENT ESOPHAGEAL VARICES IN HEPATIC CIRRHOSIS: Hugh D. Bennett, Clifford Lorentzen and Lyle A. Baker. A.M.A. Arch. Int. Med., 92:507, (Oct.), 1953.

The authors report a spontaneous disappearance of esophageal varices observed by means of repeated x-ray examinations and esophagoscopies. The phenomenon was observed in a group of patients with cirrhosis of the liver verified by clinical and laboratory examinations and liver biopsy. Whipple's concept of the variability of portal pressure in hepatic cirrhosis was confirmed by direct measurement of the portal venous pressure at the time of laparotomy for shunt operations. Normal values were obtained in several patients with recurrent hematemeses and other signs of previously elevated pressure. The following factors were suggested as causes of temporary or permanent disappearance of esophageal varices: coexisting esophagitis may aggravate varices which may subside after disappearance of this inflammation. Esophagitis and esophageal ulcerations may eliminate varices causing thrombus formation or mediastinitis. Periesophageal collateral circulation may develop and produce collapse of varices, improvement of liver function by conservative therapy may restore normal portal circulation.

H. B. EISENSTADT

CLINICAL OBSERVATIONS ON THE FATTY LIVER: Carroll M. Leevy, Myra R. Zinke, Thomas J. White and Angelo M. Gnassi. A.M.A. Arch. Int. Med., 92:527, (Oct.), 1953.

Etiological factors, clinical and biochemical findings, response to treatment and sequelae of 102 patients with fatty metamorphosis of the liver proved by aspiration biopsy are reported. A faulty diet consisting principally of carbohydrates and deficient in protein had been taken by all of them. Anorexia, alcoholism, gastrointestinal diseases, diabetes mellitus and chemical intoxications were contributing factors to the development of fatty livers. Physical examination showed hepatomegaly in almost all cases, while hepatic tenderness, jaundice, ascites, edema, spider angiomata and splenomegaly were only occasionally present. The most frequent biochemical abnormalities were alteration of plasma protein, B.S.P. retention, elevated serum bilirubin and serum cholesterol. Treatment with high protein, low fat diet and bed rest transformed a severe fatty liver into a normal one within 6 weeks. The addition of multivitamin preparations, choline, methionine, and Vitamin B_{12} did not shorten this period and was only important in patients with anorexia or systemic disease interfering with nutrition. Patients who continued to use alcohol and to eat poorly showed a transformation of the fatty liver into portal cirrhosis within a few years, while cooperative patients encountered a complete clinical, biochemical, and histiological recovery.

H. B. EISENSTADT

PANCREAS

ROENTGEN CONFIGURATION OF THE DUODENOJEJUNAL AREA IN CARCINOMA OF THE PANCREAS: R. A. Sifre, E. S. Stenberg and L. D. Graybill. Geriatrics, 8:486-493, (Sept.), 1953.

Problems in the diagnosis of carcinoma of the pancreas are discussed and there is a review of the literature concerning radiologic changes in pancreatic malignancy.

Out of 59 cases of pancreatic carcinoma diagnosed over a 10-year period, roentgenograms had been made on 34, of which 16 showed findings suggestive of pancreatic carcinoma. A new roentgenographic sign is stressed, consisting of lowering of the duodenojejunal angle with the loss of its normal acuity. Instead of the junction being located at the superior border of the second lumbar veterbra, it was found to be displaced to the level of the intervertebral space between L-2 and L-3 or below, and the angle was obtuse instead of acute. X-rays are presented demonstrating the roentgenographic changes in cases of pancreatic carcinoma.

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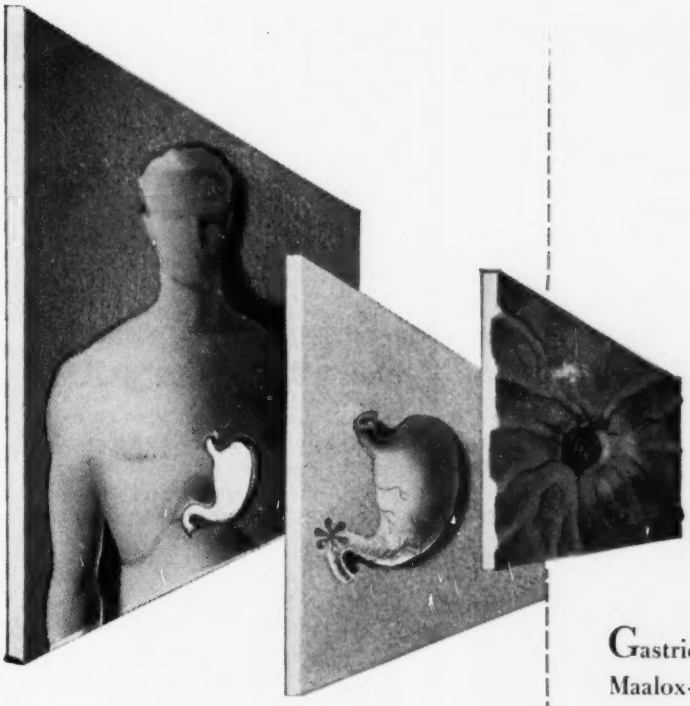

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